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Table Of Contents

The Policy Dimensions and Regulatory Landscape of Artificial Intelligence Governance By Preesha Juyal

Abstract

Artificial Intelligence (AI) has emerged as a transformative force, permeating diverse sectors of society and fundamentally reshaping our interactions with technology. With its remarkable capacity to process vast volumes of data, recognize patterns, and make autonomous decisions, AI holds immense potential for driving societal progress. However, the rapid advancement of AI has outpaced the ability of legal and regulatory frameworks to effectively govern its deployment. While traditional legal principles can provide a starting point for governing AI, they often fall short in addressing the distinctive characteristics and implications of this technology. Existing laws and regulations struggle to keep up with the swift deployment of AI systems, leaving a regulatory void that poses risks to individuals and society. Unregulated or inadequately regulated AI applications can give rise to potential harm and ethical dilemmas. This research paper undertakes a thorough analysis of the existing and proposed frameworks in the field of AI governance, focusing on their legal and policy dimensions. Through an examination of the strengths, weaknesses, and gaps present in current regulatory initiatives, the paper aims to make a meaningful contribution to the ongoing discourse on effective AI governance. Ultimately, this paper strives to offer valuable insights and recommendations for policymakers, researchers, and stakeholders, with the ultimate goal of promoting responsible AI practices and safeguarding societal interests in the development and deployment of AI technologies.

Keywords: Algorithmic Accountability, Algorithmic Transparency, Artificial Intelligence, Autonomous Systems, Bias Mitigation, Data Governance, Risk Assessment

Introduction

AI governance is a comprehensive framework that encompasses a multitude of rules, principles, and policies designed to steer the development, deployment, and utilization of AI technologies. Its primary objective is to ensure that these advancements are aligned with the fundamental values and goals of society. AI governance takes into account a wide array of factors, such as ethical considerations, legal implications, societal impact, economic ramifications, and technological facets. By striking a delicate equilibrium between fostering innovation and safeguarding individual rights, AI governance aims to effectively regulate the rapidly evolving field of AI. AI governance can be best understood by acknowledging the multidimensional nature of AI itself. AI encompasses a wide spectrum of technologies, algorithms, and systems that enable machines to perform tasks with varying levels of autonomy and intelligence, often simulating human cognitive functions. These can include but are not limited to machine learning algorithms, neural networks, natural language processing, computer vision, and robotics. Given the intricacy and diversity of AI applications, as well as their potential societal consequences, it has become imperative to establish an exhaustive governance

framework that addresses the challenges unique to the field of AI. The governance of AI entails the active participation of a wide range of stakeholders who assume crucial roles in shaping policies and regulations that foster the responsible development and deployment of AI technologies. The following table provides an overview of the stakeholders engaged in AI governance, showcasing their participation, roles, interests, and illustrative examples within the realm of AI.

Figure 1: Key Stakeholders in AI Governance

Stakeholder	Involvement	Roles and Interests	Examples
Government Agencies	Formulating policies and regulations	- Balancing innovation with societal concerns - Enacting legislation for AI governance	United States Federal Trade Commission (FTC), European Commission
Industry and Technology Companies	AI development and deployment	- Shaping the trajectory of AI technologies - Balancing commercial interests with public trust and ethical considerations	Google, Microsoft, IBM
Civil Society Organizations	Representing diverse stakeholder interests	- Advocating for consumer rights - Contributing to public dialogue	Electronic Frontier Foundation (EFF)
Research Institutions	Conducting interdisciplinary research	- Generating knowledge and insights on legal, ethical, and social implications of AI	Berkman Klein Center for Internet, Oxford Internet Institute
International Organizations	Facilitating global discussions and coordination	- Developing guidelines for AI development - Coordinating multistakeholder initiatives	United Nations (UN), World Economic International Organization for Standardization (ISO)

Multistakeholder Initiatives	Collaborating on AI governance disputes	- Engaging diverse stakeholders	Global Partnership on Artificial Intelligence (GPAI)

Legal and Policy Dimensions–Data Protection

In the context of AI governance, data protection assumes a crucial role in safeguarding individual privacy rights, ensuring fair and lawful processing of personal data, and mitigating potential risks associated with AI technologies. The utilization of vast amounts of data, including personal information, by AI systems raises significant legal and ethical considerations. Data protection encompasses a set of practices and regulations designed to protect individuals' personal data from unauthorized access, use, or disclosure. It includes principles such as transparency, purpose limitation, data minimization, accuracy, storage limitation, and accountability. The importance of data protection is amplified by the data-driven nature of AI algorithms and the potential impact of AI systems on individuals' privacy and fundamental rights. Ensuring data protection in AI systems presents distinct challenges that require thorough consideration to address potential risks and uphold individuals' privacy rights. AI systems heavily rely on data for training and enhancing their performance. However, it is crucial to navigate the inherent tension between accessing and utilizing data while upholding privacy principles. A prominent example of a comprehensive data protection framework is the General Data Protection Regulation (GDPR), implemented by the European Union. The following table highlights prominent provisions of the GDPR, along with their descriptions.

Figure 2: Key Provisions of GDPR

Provision	Description
Lawful Basis	Specifies the legal grounds for processing personal data, such as consent or legitimate interests
Data Subject Rights	Grants individuals' rights over their personal data, including access, rectification, and erasure
Data Protection Officer	Requires organizations to appoint a Data Protection Officer responsible for overseeing data protection activities
Data Protection Impact Assessment (DPIA)	Obliges organizations to assess privacy risks for high-risk processing activities

Data Breach Notification	Mandates organizations to report personal data breaches to the authorities and affected individuals

Data protection laws, such as the General Data Protection Regulation (GDPR) and similar regulations worldwide, exert substantial influence on the development and implementation of AI systems. These laws emphasize the paramount importance of acquiring informed consent from individuals during the collection and processing of their personal data. AI systems must establish robust consent mechanisms that enable individuals to make well-informed decisions about the utilization of their data. Compliance with legal frameworks governing the lawful processing of personal data is a fundamental obligation for AI developers and deployers. They must align their practices with the lawful bases outlined by data protection laws. Additionally, data protection laws advocate for data minimization and purpose limitation. It is incumbent upon AI developers and deployers to limit the collection and processing of personal data to what is strictly necessary and to ensure that such data is used solely for well-defined, legitimate purposes. Data protection laws confer enhanced rights upon individuals regarding their personal data. AI developers and deployers bear the responsibility of upholding these rights, including the right to access personal data, rectify inaccuracies, and request erasure.

Liability

The rapid progress of AI technologies has introduced complex liability concerns that require meticulous examination within the realm of AI governance. With AI systems assuming autonomous decision-making and engaging in actions that have tangible repercussions, the issue of liability for these decisions and actions becomes paramount. Determining liability in cases of harm caused by AI often necessitates the application of conventional legal principles such as causation, foreseeability, and negligence. However, integrating these principles within the context of AI systems calls for a comprehensive reassessment to accommodate the distinctive attributes of AI technologies. Manufacturers and developers of AI systems may be considered primary targets for liability attribution. These entities bear significant responsibility to ensure that AI systems are designed, developed, and deployed with adequate safeguards and risk mitigation measures in place. Holding manufacturers and developers accountable for the harm caused by AI technologies serves as a powerful incentive for the adoption of ethical practices and the integration of safety mechanisms. Nevertheless, users of AI systems may also bear a measure of responsibility in instances of AI-generated harm. Users have an obligation to exercise responsible usage of AI systems and ensure that their usage aligns with appropriate contexts. Negligent or improper use of AI systems can contribute to adverse outcomes. Various legal frameworks play a vital role in addressing liability within AI governance. These frameworks encompass tort law, contract law, product liability law, regulatory standards, and proportional liability, collectively forming the foundation for determining liability and allocating responsibility in cases involving harm caused by AI systems. However, the distinctive

characteristics of AI, including its non-transparency and autonomous decision-making capabilities, demand a careful examination of how traditional liability frameworks are applied in practice. The following table presents the existing legal framework in AI governance that evaluates liability, highlighting its application, strengths, and weaknesses.

Figure 3: Existing Legal Frameworks for Liability Evaluation

Legal Framework	Application	Strengths	Weaknesses
Tort Law	Determines liability for harm caused by negligence	Well-established principles of liability	Challenges in attributing liability to non-human agents
Contract Law	Governs liability in contractual agreements	Clarity in determining contractual obligations	Limited scope regarding addressing any third-party harm
Product Liability	Addresses liability of manufacturers and developers	Encourages product safety and quality control	Difficulty in applying traditional product liability to AI systems
Regulatory Standards	Sets specific legal standards and obligations for AI	Provides clear guidelines for responsible AI use	Challenges in keeping pace with rapid technological advancements
Proportional Liability	Assigns liability proportionally based on degrees of contribution	Fair distribution of liability based on responsibility	Complexities in determining degrees of contribution

Case Study: Tesla Autopilot Accident Liability

Autonomous vehicles serve as a compelling example that highlights the intricate nature of liability within the realm of AI governance. A recent case involving a Tesla Model S operating in Autopilot mode and a tragic accident in 2021 serves as a poignant reminder of the ongoing challenges in determining liability for autonomous vehicle accidents. Diligent investigations are currently focused on discerning the respective responsibilities of Tesla as the manufacturer, the driver as the vehicle operator, and the AI technology itself. This incident has underscored the pressing need for more explicit guidelines and comprehensive regulations that can effectively address liability concerns in the context of autonomous vehicle accidents. Such guidelines should

take into account critical factors such as the level of autonomy, the role of human oversight, and adherence to stringent safety standards.

Intellectual Property

The intersection of AI and intellectual property (IP) presents captivating challenges and opportunities within the domain of AI governance. Intellectual property rights, including patents, copyrights, trade secrets, and trademarks, play a pivotal role in incentivizing innovation, safeguarding creators' rights, and stimulating economic advancement. In the context of AI, these IP rights require a reevaluation of traditional patent frameworks due to the distinct capabilities and autonomous nature of AI systems. Patentability typically relies on criteria such as novelty, inventive step, and industrial applicability. However, applying these criteria to AI-generated inventions raises inquiries about the degree of human involvement, the level of AI autonomy, and the nature of inventive steps in the presence of machines. A crucial aspect of patenting AI-generated inventions is determining the extent of human participation in the inventive process. Patent systems commonly require a human inventor who has made a non-obvious and significant contribution to the invention. As AI systems progressively gain autonomy and generate inventions without direct human intervention, the matter of attribution and recognition becomes intricate. Furthermore, the concept of inventive step or non-obviousness, a fundamental criterion for patentability, poses challenges in the context of AI-generated inventions. Assessing whether an AI system's output is non-obvious compared to existing knowledge presents difficulties, given that AI algorithms can process vast amounts of data and identify patterns that humans may overlook. In copyright law, authorship and ownership are typically attributed to human creators, raising questions about whether AI can be recognized as a copyright holder and how to establish ownership of works generated by AI systems. The distinction between human authorship and AI authorship is a critical aspect of copyright ownership in AI-generated works. Determining copyright ownership requires careful consideration of the level of human involvement and the nature of the collaboration between AI systems and human creators. Some jurisdictions are exploring the complexities of defining authorship and developing legal frameworks to recognize AI as a potential creator. Others focus on clarifying the role of human creators in the creative process when AI systems are involved, aiming to establish guidelines that appropriately reflect human contributions and intentions in collaboration with AI systems. The table below presents several examples of jurisdictions in different countries that have either explored or implemented specific guidelines or regulations concerning the copyright of AI-generated works.

Figure 4: Copyright Jurisdictions in Different Countries

Country	Approach
United States	Works generated by AI systems without human involvement or creative contribution are not eligible for copyright protection.

United Kingdom	AI-generated works created without human intervention or control do not qualify for copyright protection unless there is a sufficient level of human involvement in the creative process.
Canada	Works solely generated by an AI system, without human intervention or creative contribution, would not be eligible for copyright protection.
Japan	AI-generated works lacking human intervention or creative involvement would not qualify for copyright protection unless a human author significantly contributes to their creation.

International Cooperation

The global impact of AI necessitates collaborative efforts among countries, organizations, and stakeholders to develop common standards, guidelines, and policies for responsible and ethical development and deployment. Harmonized regulations and standards enable international trade, cooperation, and the exchange of AI technologies, knowledge, and expertise by removing redundant compliance requirements and facilitating cross-border collaboration.

Analysis of Existing Regulatory Frameworks–European Union

The European Union (EU) has taken a leading role in developing robust regulatory frameworks to govern AI technologies. In April 2021, the European Commission introduced the proposed AI Act, which seeks to establish a harmonized legal framework for AI governance within EU member states. The table below highlights the key ethical, legal, and technical provisions of the AI Act. The following table highlights prominent provisions of the AI Act, along with their descriptions.

Figure 5: Key Provisions of the AI Act

Key Provisions	Descriptions
Risk-Based Approaches	- Categorizes AI systems based on risk levels - Allows for tailored regulation based on the potential risks associated with each system
Human Oversight and Accountability	- Mandates high-risk systems to establish risk management systems with human-in-the-loop mechanisms - Ensures humans retain control and responsibility over critical decisions
Prohibited Practices	- Identifies and prohibits AI practices that are

	contrary to EU values and fundamental rights - Examples include social scoring, AI-enabled biometric identification, and subliminal techniques for human manipulation
Transparency and Traceability	- Requires detailed documentation of AI system capabilities, limitations, and potential biases

On June 14, 2023, the European Parliament passed the AI Act with a large majority, marking an important milestone in the legislative process. The Act, now moving towards the final Trilogue stage, holds the potential to bring about substantial changes in AI governance within the European Union. If implemented, it would establish clear guidelines for transparency, accountability, and ethical standards in AI systems while defining legal obligations for developers and users. Additionally, the Act seeks to foster a unified market for AI technologies by harmonizing regulations across EU member states. Its impact transcends regional boundaries, as it can serve as a reference and influence global discussions on AI governance, potentially shaping the approaches taken by other countries.

Addendum*:* It is important to note that an examination of the General Data Protection Regulation's (GDPR) impact on AI governance was conducted earlier in this paper.

United States

In the United States, federal agencies play a significant role in shaping the regulatory landscape of AI governance, focusing on specific aspects of AI technologies. While the regulatory efforts in the U.S. are currently sector-specific rather than comprehensive at the federal level, they demonstrate the government's acknowledgment of the importance of oversight and regulation in promoting the responsible development and deployment of AI systems. The following table highlights the focus areas and key initiatives of federal agencies involved in AI governance.

Figure 6: Federal Agencies Involved in AI Governance

Federal Agency	Focus Area	Key Initiatives
Federal Trade Commission (FTC)	Consumer Protection	- Addressing consumer protection issues including discriminatory practices - Monitoring practices to ensure compliance with

		existing laws
National Institute of Standards and Technology (NIST)	Technical Standards and Guidelines	- Developing standards for data quality, interoperability, and algorithmic transparency
National Highway Traffic Safety Administration (NHTSA)	Regulation of AI in the Automotive Industry	- Developing guidelines for autonomous vehicles - Fostering innovation and ensuring safety through industry collaboration

In recent years, various states in the United States have implemented initiatives to address the governance of AI technologies within their jurisdictions, aiming to augment federal regulations and provide additional guidance for responsible AI development and deployment. The following table highlights the key initiatives of regional agencies involved in AI governance.

Figure 7: Regional Agencies Involved in AI Governance

State	Initiative Name	Key Initiatives
New York	Automated Decision Systems Task Force	- Reviews the use of AI and automated decision-making in city agencies
California	California Consumer Privacy Act (CCPA)	- Gives individuals rights to access, correct, and delete personal data
Washington	Algorithmic Accountability Act	- Regulates the use of algorithms to mitigate potential biases and discrimination

The impact of these initiatives is twofold. Federal initiatives provide a comprehensive framework for AI governance, ensuring nationwide compliance and addressing overarching concerns. Meanwhile, state-level initiatives add an additional layer of protection and regulations, catering to the unique needs and priorities of individual states. These initiatives have resulted in heightened transparency in data practices, strengthened consumer rights regarding personal information, and imposed responsibilities on businesses to handle data responsibly.

China

The regulatory landscape in China is a testament to the government's unwavering commitment to nurturing AI development while prioritizing ethical and responsible use. The comprehensive set of regulations and guidelines within China's AI regulatory framework exemplifies the government's dedication to addressing critical aspects of AI development, such as data security, algorithm evaluation, and ethical considerations. These measures lay a solid foundation for the responsible and ethical utilization of AI technologies across diverse sectors throughout the country. China has notably placed significant emphasis on the establishment of national standards for AI technologies through its National Standardization Plan for AI. The following table highlights key aspects of the National Standardization Plan, along with their descriptions.

Figure 8: Key Aspects of the National Standardization Plan

Aspect	Description
Data Security	Addresses requirements for data collection, storage, processing, and sharing in AI systems
Algorithm Evaluation	Provides guidelines for evaluating algorithms based on factors such as accuracy and fairness
Ethical Guidelines	Incorporates ethical considerations into AI development, promoting fairness and privacy

Similarly, the Cyberspace Administration of China (CAC) has taken a proactive approach by publishing AI Ethics Guidelines aimed at fostering the responsible and ethical use of AI technologies. These guidelines serve as an important reference for organizations and individuals working with AI, promoting adherence to common benchmarks and guidelines that prioritize consistency, interoperability, and transparency within the AI landscape. By upholding ethical principles and societal values, China endeavors to cultivate an environment that nurtures innovation while ensuring the responsible and ethical deployment of AI technologies. The following table highlights key aspects of the AI Ethics Guidelines, along with their descriptions.

Figure 9: Key Aspects of the AI Ethics Guidelines

Aspect	Description
Fairness and Non-discrimination	Emphasizes the importance of developing AI systems that treat individuals fairly and without bias

Transparency and Explainability	Promotes transparency and explainability of AI systems, encouraging clear documentation and disclosure of operations
Privacy and Security	Highlights the significance of protecting personal data and ensuring compliance with data protection regulations

The National Standardization Plan for AI in China primarily concentrates on technical standards and standardization, serving as a crucial pillar in shaping the regulatory landscape for AI. This plan focuses on ensuring technical quality, consistency, and interoperability across AI systems and applications. On the other hand, the AI Ethics Guidelines complement the technical standards by prioritizing ethical principles and providing valuable guidance for responsible AI development and deployment. These guidelines play a vital role in promoting ethical considerations and fostering the responsible use of AI technologies in various sectors. By combining both the National Standardization Plan and the AI Ethics Guidelines, China establishes a comprehensive framework that addresses both technical and ethical dimensions, striving for harmonious integration of innovation, technical excellence, and ethical values in the AI ecosystem.

Conclusion

The analysis of existing and proposed regulatory frameworks for AI governance underscores the critical importance of effective governance in addressing the legal, ethical, and social implications of AI technologies. As the landscape of AI continues to evolve, it presents numerous challenges that necessitate comprehensive and well-designed governance approaches. These challenges encompass areas such as data protection, liability attribution, intellectual property, and international cooperation. Effective AI governance plays a pivotal role in fostering innovation, ensuring accountability, protecting individual rights, and maintaining public trust. It requires a balanced approach that promotes responsible AI development while mitigating potential risks and harms. Clear regulations, comprehensive standards, and robust enforcement mechanisms are indispensable components of effective AI governance. In conclusion, effective AI governance is vital for harnessing the vast potential of AI while proactively addressing associated risks. By adopting a comprehensive and forward-looking approach, policymakers, organizations, and researchers can contribute to the development of robust regulatory frameworks that promote responsible AI practices, protect societal interests, and ensure the equitable and sustainable realization of the benefits AI can offer.

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How Has the Lack of Representation of Women in Clinical Trials Resulted in their Inadequate Treatment of Prescription Medication By Aanya Arora

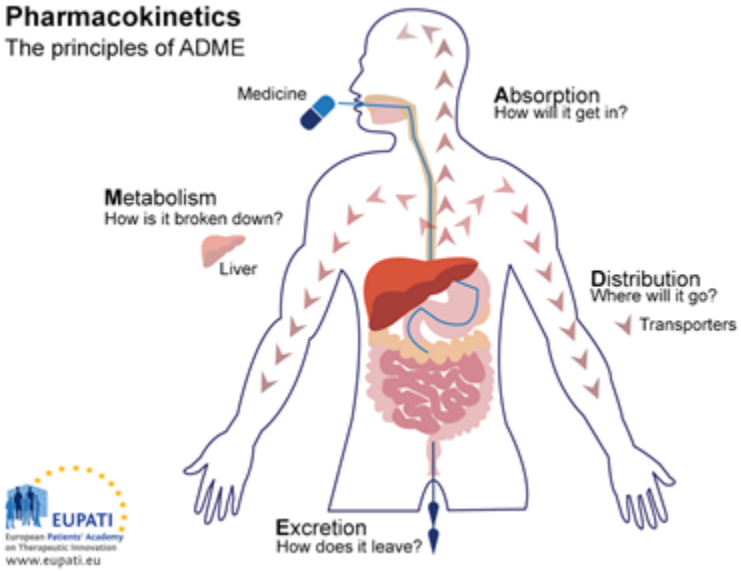
Introduction

In the wake of the introduction of Coronavirus-19 (COVID-19) vaccines, there have been reports indicating a relatively higher incidence of side effects among women compared to men. Additionally, there have been anecdotal accounts of unlisted side effects, particularly related to the menstruation cycle. The phenomenon of encountering challenges and concerns related to the administration of COVID-19 vaccines is not an isolated occurrence, but rather a recurring pattern observed in the context of various pharmaceutical interventions. This research paper provides an overview of commonly prescribed drugs that are used by both men and women, with a focus on the differential impact of these drugs on the two genders. Specifically, it examines the occurrence of more severe side effects in women as compared to men. The underrepresentation of women in clinical trials has been identified as a contributing factor that can potentially have negative implications for women's health. The construction of a drug involves several phases and factors that necessitate careful consideration. During the testing process, the drug is typically evaluated on what is commonly referred to as the "average human body," which predominantly represents the male body. Hence, it can be argued that the suitability of these drugs for women is questionable. The present argument posits that a notable factor contributing to the divergence in side effects experienced by men and women is the exclusion of women from the drug synthesis process. This exclusion, it is argued, has significant implications for women's health. This lack of representation of women in clinical trials has resulted in inadequate treatment for women when it comes to prescription medication.

Background

The process of drug synthesis involves multiple stages, including pre-clinical testing and clinical trials. During pre-clinical testing, drugs are typically evaluated for efficacy and safety using animal models before moving on to clinical trials involving human subjects. These clinical trials are essential for determining the safety and effectiveness of drugs in humans. During human trials, there are three main stages: Phase 1, Phase 2, and Phase 3. During Phase 1, the drug is tested on a small group of healthy volunteers to evaluate its safety and determine the optimal dosage. During Phase 2, the drug is tested on a larger group of patients to assess its effectiveness and further evaluate its safety. Phase 3 involves testing the drug on a larger population to confirm its effectiveness, monitor side effects, and compare it to existing treatments. The lack of representation of women in clinical trials has been a longstanding issue. According to Pinnow et al, only 32.5% of participants in Phase I trials approved by the FDA between 2006 and 2007 were women ((Sandberg & Verbalis, 2013)). This underrepresentation of women in clinical trials raises concerns about the generalizability and effectiveness of drugs for women. Furthermore, a study conducted by Yang et al found that although there has been

progress in including women in Phase III clinical trials regulated by the FDA, there is still significant variation in female participation by class of drug, indicating a continued lack of comprehensive representation ((Sandberg & Verbalis, 2013)). Given this lack of representation, it is not surprising that women may experience different side effects and varying levels of efficacy compared to men when using certain medications. Therefore, the exclusion of women from the drug synthesis process can have profound consequences on women's health.
When metabolizing a drug the human body goes through a process called pharmacokinetics, which involves absorption, distribution, metabolism, and elimination of the drug. Pharmacokinetics plays a crucial role in determining both the efficacy and safety of a drug. Understanding the pharmacokinetics of a drug is imperative to optimize its dosage and administration, minimize potential side effects, and ensure that the drug reaches the desired therapeutic levels in the body. When processing a drug many differences in the male and female body can impact pharmacokinetics ((Ekong et al., 2015)).



((Introduction to Pharmacokinetics: Four Steps in a Drug's Journey Through the Body, 2021))

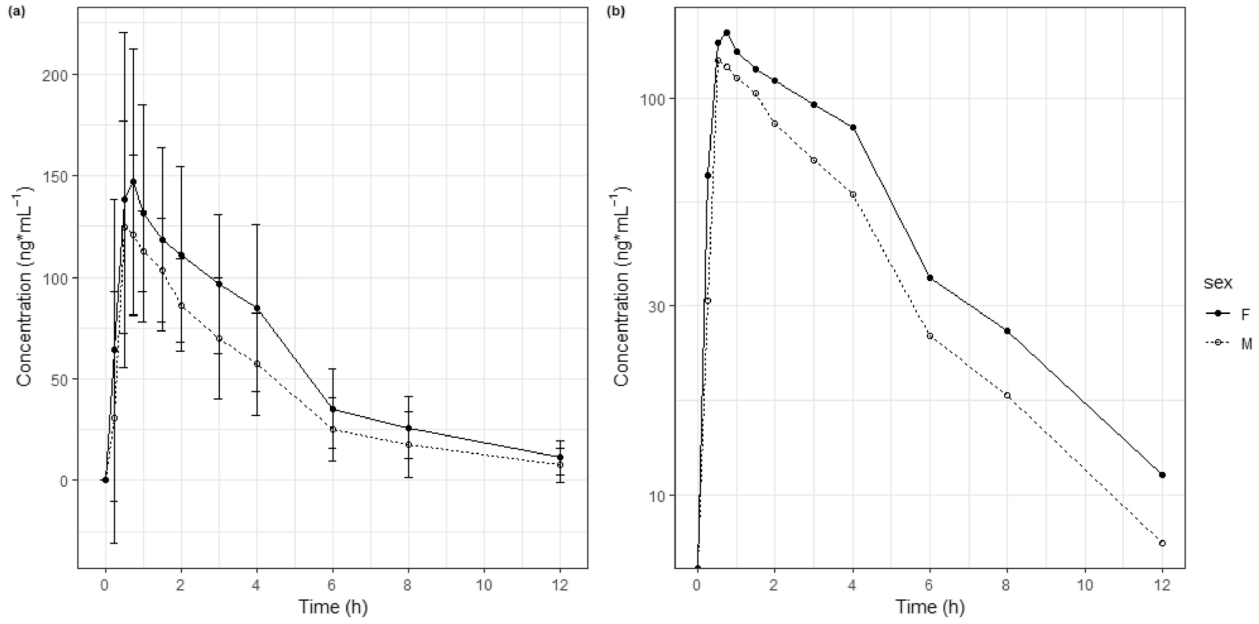
For example, there are well-established differences in drug-metabolizing capacity between males and females. These differences can lead to variations in drug metabolism, which may result in different levels of drug exposure and response between men and women. These differences in drug-metabolizing capacity between males and females can have direct implications for medication efficacy and safety. Sex differences in drug metabolism can arise from variations in the expression of hepatic enzymes such as cytochromes P450, sulfotransferases, glutathione transferases, and UDP-glucuronosyltransferases ((Farid et al., 2023)). These enzymes play a crucial role in the metabolism of drugs, steroids, fatty acids, and environmental chemicals. Numerous studies have demonstrated that the activity levels of these enzymes can vary between males and females. By affecting how drugs are processed and eliminated from the body, these sex-based metabolic differences contribute to variability in

pharmacokinetics. These differences in drug metabolism can lead to variations in drug exposure and response between men and women. In addition to differences in drug metabolism, other factors can contribute to sex-dependent pharmacokinetics factors such as organ size, body composition (higher percentage of body fat in females), and renal function (lower glomerular filtration rate in females) have also been identified as potential contributors to sex-dependent pharmacokinetics ((Lakmichi et al., 2011)). Furthermore, endogenous and exogenous hormones play a significant role in shaping sex differences in pharmacokinetics. This highlights both a need for further research exploring sex-specific effects on drug responses and improved representation of women participants across clinical trials ((Lynch, 2022)).

The differences between the sex's anatomy and physiology, specifically in terms of drug metabolism and pharmacokinetics, are important factors that contribute to individual variances in toxicity and therapeutic response ((Almeida et al., 2016)). These differences highlight the need for personalized medicine approaches that consider sex as a factor in drug development, prescribing, and dosing. This paper highlights examples of popular drug cases in which gender differences in drug metabolism have been observed, illustrating the importance of considering sex as a factor in pharmacokinetics.

Drug Examples Illustrating Gender Differences in Drug Metabolism Pharmacokinetics

Zolpidem is a commonly prescribed sleep aid and exhibits sex-dependent differences in drug metabolism. Studies have shown that women metabolize Ambient at a significantly slower rate compared to men, leading to higher drug concentrations, increased risk of adverse effects in female patients such as excessive sedation or impaired cognitive function, and higher blood levels of the drug in women ((Penaloza et al., 2020)). This is primarily due to the expression of the hepatic enzyme CYP3A4, which is responsible for metabolizing Zolpidem. It has been found that women have a higher expression of CYP3A4 compared to men, resulting in slower metabolism and clearance of the drug from their bodies ((Vries & Forger, 2015)).



((Yoon et al., 2021))
The figure above presents a study conducted on the effect of gender on the pharmacokinetics of Ambient. During this study, the drug (zolpidem) was administered to both male and female participants, and blood samples were collected at various time points to measure drug concentrations.

- Zolpidem was rapidly absorbed, with maximum concentrations (Cmax) reached within 1 hour in most subjects.
- The median time to reach Cmax (Tmax) was slightly longer in females (1.1 hours) compared to males (0.9 hours).
- Mean plasma levels of zolpidem were consistently higher in female subjects at all time points.
- Female subjects had higher mean Cmax, AUC0-12h (area under the concentration-time curve from 0 to 12 hours), and AUCinf (area under the concentration-time curve extrapolated to infinity) values compared to male subjects.
- The increases were approximately 10.9%, 31.0%, and 32.5% respectively. Although the p values did not show significant differences, the confidence intervals (geometric mean ratios) for AUC0-12h and AUCinf did not include 1.000, **suggesting higher exposure in females.**

These findings suggest that women experience higher plasma concentrations of zolpidem, leading to longer periods of impairment compared to men when exposed to equal doses ((Jenkins et al., 2016)).

Case 2: Oral Anticoagulant Medications

The use of anticoagulant medications is critical for the prevention and treatment of various cardiovascular conditions, including atrial fibrillation, deep vein thrombosis, and pulmonary embolism. Understanding the sex differences in the pharmacokinetics of anticoagulant medications is crucial for optimizing their efficacy and minimizing potential risks. For example, several studies have indicated that women may require lower doses of certain anticoagulant medications, such as warfarin, compared to men, due to differences in drug metabolism and clearance rates.

A study conducted investigated the use of oral anticoagulants (OAC) among men and women with atrial fibrillation (AF). Results showed that women were older and had a higher median estimated thromboembolic risk compared to men in the study cohort of 691,906 patients with AF. Interestingly, women showed lower use of OACs, even though they were at greater risk of thromboembolic events than men. The study presents several possible reasons for the lower use of oral anticoagulation (OAC) in women with atrial fibrillation (AF): ((MSCS et al., 2017))

- Under recognition of Thromboembolic Risk: Healthcare providers may underestimate the thromboembolic risk in female patients. While women with AF have a higher risk of stroke, it may not be acknowledged sufficiently.

- Concerns About Bleeding: There could be concerns about increased bleeding risk, particularly with warfarin, for female patients.

These concerns may stem from the higher rates of bleeding observed among women compared to men when taking oral anticoagulants, with studies showing a 20% higher risk of bleeding in women. ((Bleeding Issues in Women Under Oral Anticoagulation - PubMed, n.d)) Women with atrial fibrillation (AF) are at a disadvantage because they are less likely to receive oral anticoagulation (OAC) than men, despite having a higher risk of stroke. This is significant because OAC therapy is crucial in preventing strokes in patients with AF. The underuse of OAC in women can therefore lead to higher incidences of stroke, which can result in serious health consequences, including death or long-term disability. Additionally, the study specifies that the underrecognition of the female sex as a thromboembolic risk factor does not fully explain these differences, **hinting at systemic biases in medical care.**

Overall, these disparities underscore the need for interventions targeted at increasing appropriate OAC use, especially among women. The findings of this study are consistent with previous research that has shown a higher risk of thromboembolism in women with AF who do not receive oral anticoagulation.

Case 3: Antidepressants

Antidepressants are commonly prescribed medications for the treatment of depression and other mental health disorders. They work by balancing chemicals in the brain called neurotransmitters, which are involved in mood regulation. However, there is evidence to suggest that women may have different responses to antidepressant medications compared to men. ((Bies et al., 2003))

For example, women may metabolize antidepressants differently or have different sensitivities to side effects. These factors can influence the effectiveness and tolerability of antidepressant treatment in women. These gender differences in response to antidepressants highlight the importance of considering sex as a factor when prescribing these medications. This could be because there may be hormonal and physiological factors at play that contribute to the differential response, such as

- Symptom Presentation: Women often present with atypical features of depression. They exhibit more reverse vegetative symptoms like hyperphagia (excessive eating), hypersomnia (excessive sleep), and weight gain.
- Antidepressant Response: Women exhibit distinct differences in metabolism of and response to antidepressants when compared to men. For example, premenopausal women respond better to Monoamine Oxidase Inhibitors (MAOIs) than to Tricyclic Antidepressants (TCAs). However, their response to TCAs is often not distinguishable from a placebo effect.
- Age and Hormonal Factors: The response to antidepressants also changes with age and hormonal situation, with differences seen when comparing pre- to post-menopausal women. For instance, younger women can respond differently to antidepressants due to

hormonal fluctuations. Estrogen effects on mood in postmenopausal women warrant investigation.

- Pregnancy and Childbearing: Depression in women of childbearing age presents unique challenges. For example, they were previously excluded from most pharmacokinetic studies of antidepressant medication, despite the significant number of these women who have depression. Moreover, certain antidepressants need to be avoided during pregnancy due to potential teratogenic effects.
- Lack of Gender-Specific Research: There is a paucity of research on gender-specific differences related to antidepressants. This represents an understudied and necessary research area. Antidepressants used for treating women are conventionally developed and tested primarily in men, which potentially overlooks essential pharmacokinetic and pharmacodynamic differences.

Case 4: COVID-19 Vaccines

COVID-19 vaccines have been developed and approved for use on a global scale, but it is crucial to evaluate potential gender differences in vaccine response. Understanding how men and women may differ in their response to COVID-19 vaccines is essential for optimizing vaccination strategies and ensuring equitable distribution of protection against the virus to all individuals.

Studies have shown that several hormonal and psychological factors could contribute to the gender disparity in COVID-19 vaccine adverse effects.
In terms of hormonal factors, women's sex hormones, such as estradiol, have been shown to increase the formation of antibodies and thus contribute to a stronger immunological response. On the other hand, testosterone, which is predominantly found in males, may act oppositely by decreasing immune responses but simultaneously increasing male susceptibility to viral infection. Psychological and societal factors also play a role in understanding gender differences when it comes to reporting adverse effects from vaccines. The social structure of masculinity and femininity can influence health-seeking behaviors differently between men and women; for instance, women are more likely than men to seek medical aid promptly and therefore may report adverse effects more frequently. Furthermore, biases or gender-related behaviors around health reporting and treatment-seeking can lead to disparities in how reported side effects are perceived or acknowledged between genders. It should be noted that these various factors interact with each other in complex ways that ultimately shape the occurrence, severity, and reporting of adverse effects following COVID-19 vaccination. ((AlQazaz et al., 2022))

Overall, it is essential to consider and examine potential gender differences in vaccine response when evaluating the safety and efficacy of COVID-19 vaccines. Furthermore, research has demonstrated that women are at a considerably higher risk of experiencing adverse effects following COVID-19 vaccination compared to men. Therefore, understanding the underlying reasons for this gender disparity is crucial to ensure that vaccination strategies are optimized and equitable.

Conclusion

The present study delved into the matter of inadequate female participation in clinical trials and the potential repercussions of this disparity. As a result, the following conclusion has been drawn. The reasons for the inadequate representation have been deliberated upon and emphasized as a crucial matter that requires attention to guarantee the safety and efficacy of medications for all patients. The dissimilarities in anatomy and physiology between men and women necessitate the incorporation of such distinctions in the development of pharmaceuticals. Throughout history, clinical trials have often excluded women based on potential harm to fetuses, resulting in a dearth of information regarding the safety and efficacy of pharmaceuticals for women. To tackle this matter, it is imperative to devise alternative pharmaceuticals that consider the distinctive physiology of women. One potential strategy for administering medication to women is to utilize both rapid and slow-release drugs to achieve optimal dosing over a prolonged period. Dose escalation and other strategies may be implemented to ensure that women receive appropriate medication dosages tailored to their individual requirements. The FDA must enhance its cognizance regarding the potential complications linked with pharmaceuticals intended for women and implement measures to guarantee the safety and efficacy of drugs for this demographic.

Furthermore, it is imperative to incorporate a more comprehensive assessment of variables such as race, transitioning, and ethnic background to ensure that the drug synthesis procedure is more inclusive and suitable for our society.In summary, the matter of inadequate female participation in clinical trials is a significant concern that requires attention. By implementing measures to produce pharmaceuticals that are both secure and efficacious for females, we can guarantee that all recipients obtain the appropriate and merited medical attention.

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Exploring the Correlation between Ego-Dystonic Perception and Dark Triad Personality in Asian Communities By Tam Anh (Katie) Truong[1]

Summary

Ego-dystonicity is the penumbra between obsessions (typically associated with obsessive-compulsive disorder) and other distressing negative thoughts recorded in other mental disorders and non-clinical daily worries. This article focuses on under-represented non-clinical causes and explores the correlation between ego-dystonicity and the Dark Triad personalities (i.e., Psychopathy, narcissism, Machiavellianism) in Asian communities. Notably, it aims to explain whether ego-dystonic self-perception and thoughts are linked to aberrant and "unlikeable" personalities at a subclinical level, meaning the sample gathered was non-clinical, including those in the workplace or a school setting. Our survey data of 51 participants yielded weak relations but moderate correlations among ego-dystonicity and the Dark Triad personalities. We hypothesized positive correlations between ego-dystonicity and Psychopathy and Machiavellianism, respectively, and a negative correlation for narcissism. In all, the gathered data showed reasonable grounds for further scientific research. Given that the sample was relatively small and concentrated, the correlation might be more prevailing should this topic be further researched.

Introduction

The Dark Triad, made of three overlapping but distinctive personality traits: Psychopathy, Machiavellianism, and narcissism, has long been a fascination and one of the biggest mysteries of the psychiatric community. There has been a long-going debate on the origins, the causes, and most importantly, the inner workings of these traits. All three dark triad personality traits have been associated with toxic and undesirable qualities such as manipulation, callousness, and selfishness. While Psychopathy and narcissism can be clinical and are often researched in clinical samples, Machiavellianism is simply a non-clinical trait with no diagnosable disorder. However, it can present as a symptom of one. The Dark Triad is often explored for its overt behaviors that damage inter- and intrapersonal relationships. The etiology of the Dark Triad is relatively unknown due to high levels of individual differences. However, evolution, genetics, and environmental factors all shape this set of personalities (1).

Ego-Dystonicity

The Penguin Dictionary of Psychology defines ego-dystonicity as "descriptive of wishes, dreams, impulses, behaviors, etc., that are unacceptable to the ego; or, perhaps more accurately, unacceptable to the person's ideal conception of the self (2).” Consequences of these obsessions or visions are severe distress and confusion, coupled with self-deprecation as the patient seeks an understanding of these obsessions that are ego-dystonic, as the patient seeks an understanding of these obsessions that are not aligned with their perceived sense of self. Despite its importance, ego-dystonicity has not been extensively studied. The definition of the term itself was blurry and

discriminating, nowhere near enough to gauge the complexities of an individual's personality nor to encompass the relationship between thought and personality (3). There are various definitions of ego-dystonicity. One study defined ego-dystonicity as "inconsistency with one's belief system (4).". In contrast, another study defines it as "the degree that the content of the obsession is contrary to or inconsistent with a person's sense of self as reflected in his or her core values, ideals, and moral attributes (5)."

Dark Triad Personality and Ego-Dystonicity

Other non-OCD personality disorders have been assessed for their correlation with ego-dystonicity and synchronicity. Hart et al. (2018) found that PD trait expression only "harmonizes somewhat with the person and their goals (6)." An interesting finding is that antagonism and psychoticism traits from the Personality Inventory for DSM-5 (PID-5) that are considered maladaptive (7) repeatedly scored the highest in all PD-trait parameters (strategic-use perceptions; functionality perceptions; self-recrimination) (6). Also noteworthy in self-perception in the Dark Triad traits is that they tend to exhibit a weaker sense of self (8). Doerfler et al. (2021)'s study found that "[d]ark Triad traits have more state-related and fewer trait-related self-concepts, a pattern which reflects the short-term thinking of people with Dark Triad traits and their reduced access to their personality traits. Furthermore, not all subcomponents of the Dark Triad are equally predictive of weaker and more uncertain self-concepts. Although virtually all the subcomponents were significantly associated with a weaker sense of self and less self-concept clarity (8)." These findings lend credence to the aberrant and unstable nature of the Dark Triad's sense of self or personality.

Therefore, the displeasing nature of the Dark Triad could be linked to the undesirability of self-perception and inner thoughts, which has not been fully explored in the subclinical context or other personality disorders. This gap in the academic literature concerning Dark Triad personality and ego-dystonicity is the primary motivation of our research. The most significant finding in our research is the positive correlation between Psychopathy and ego-dystonicity, particularly factor (a) "degree of consistency with morals, beliefs, values, and attitudes." Therefore, we can infer that subclinical Dark Triad traits are correlated to some extent with ego-dystonicity.

Results

The self-report questionnaire containing items to measure all factors recorded in this study was distributed anonymously to random community members. This way, we ensure (a) anonymity or eliminate individualization and (b) ensure geographical and demographic diversity in our test. To test the hypotheses and research questions, we examined the correlations between all variables and conducted regression analyses with different subdimensions of ego-dystonicity. **Table 1** includes means and standard deviations for all variables and correlations. The regression results for ego-dystonicity factor 1 (EDQ(a)) are reported in **Table 2**, and factor 3 (EDQ(b)) in

Table 1. Means, SD, and Correlations of all study variables with EDQ(a) and EDQ(b).

Variable	*M*	*SD*	1	2
1. EDQ(a)	4.172	1.190	–	–
2. EDQ(b)	4.199	1.175	–	–
3. Machiavellianism	3.538	.640	.156	.169
4. Psychopathy	2.828	.571	.301*	.190
5. Grandiose Narcissism	3.430	1.351	-.130	-.129
6. Covert Narcissism	3.327	.589	.164	.050

*$p < .05$.

Table 2. Regression Analysis of Dark Triad Personality and EDQ(a).

Variable	Estimate	*SE*	95% Cl		*p*
			LL	*UL*	
Intercept	2.678	1.176	.311	5.046	.027
Machiavellianism	.014	.310	-.611	.638	.965
Psychopathy	.727	.344	.035	1.419	.040
Grandiose Narcissism	-.191	.128	-.448	.066	.141
Covert Narcissism	.013	.329	-.650	.676	.968

Table 3. Regression Analysis of Dark Triad Personality and EDQ(b).

Variable	Estimate	*SE*	95% Cl		*p*
			LL	*UL*	
Intercept	3.435	1.195	1.030	5.839	.006
Machiavellianism	.249	.315	-.386	.883	.434
Psychopathy	.460	.349	-.243	1.163	.194
Grandiose Narcissism	-.181	.130	-.442	.081	.171
Covert Narcissism	-.239	.335	-.193	.434	.478

Table 1 shows positive correlations between variables EDQ(a) and EDQ(b), with all the Dark Triad traits, were found apart from grandiose narcissism, which exhibited negative correlations in both cases. Notably, our results showed positive relationships between Psychopathy and the two subdimensions of ego-dystonicity (with EDQ(a): r=.301, p<.05; with EDQ(b): r=.190, p=.194), signifying a positive relationship between immorality of thought and psychopathic tendencies on a subclinical level. Among all three Dark Triad personality traits, Psychopathy was most strongly associated with both factors **(Figure 1)**. Additionally, we tested the relationship between Machiavellianism and both ego-dystonicity factors. While a positive correlation is present, Machiavellianism is weakly correlated with ego-dystonicity (r=.156, p=.965; r=.169, p=.434). Thus, there is no significant correlation between ego-dystonicity and this factor of the Dark Triad. The negative correlations between grandiose narcissism with two ego-dystonicity measures were not significant (with EDQ(a): r=-.130, p=.141; with EDQ(b):

r=-.129, p=.171), whereas the correlations are positive for EDQ(a) and covert narcissism **(Figure 2)**.

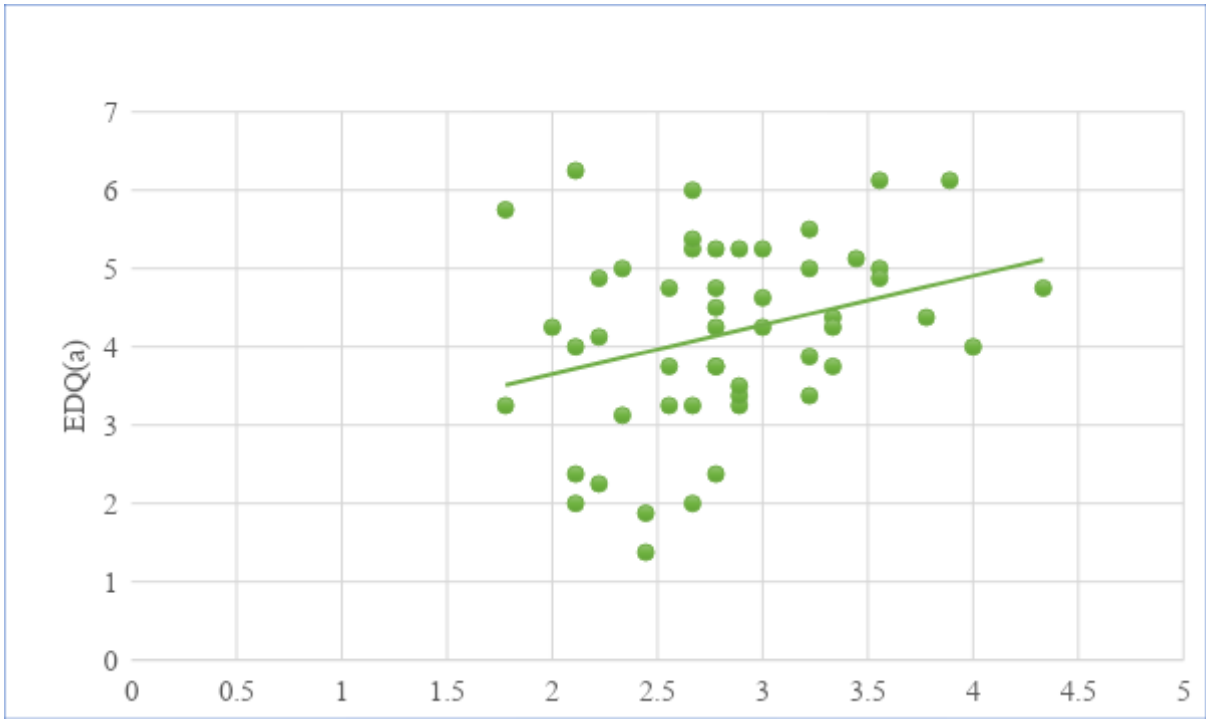

Figure 1. Correlation between Psychopathy and Ego-dystonicity factor 1. Scatter plot showing quoted ratings by participant for EDQ(a) and Psychopathy taken from the online survey. Line of best fit shows a moderate correlation.

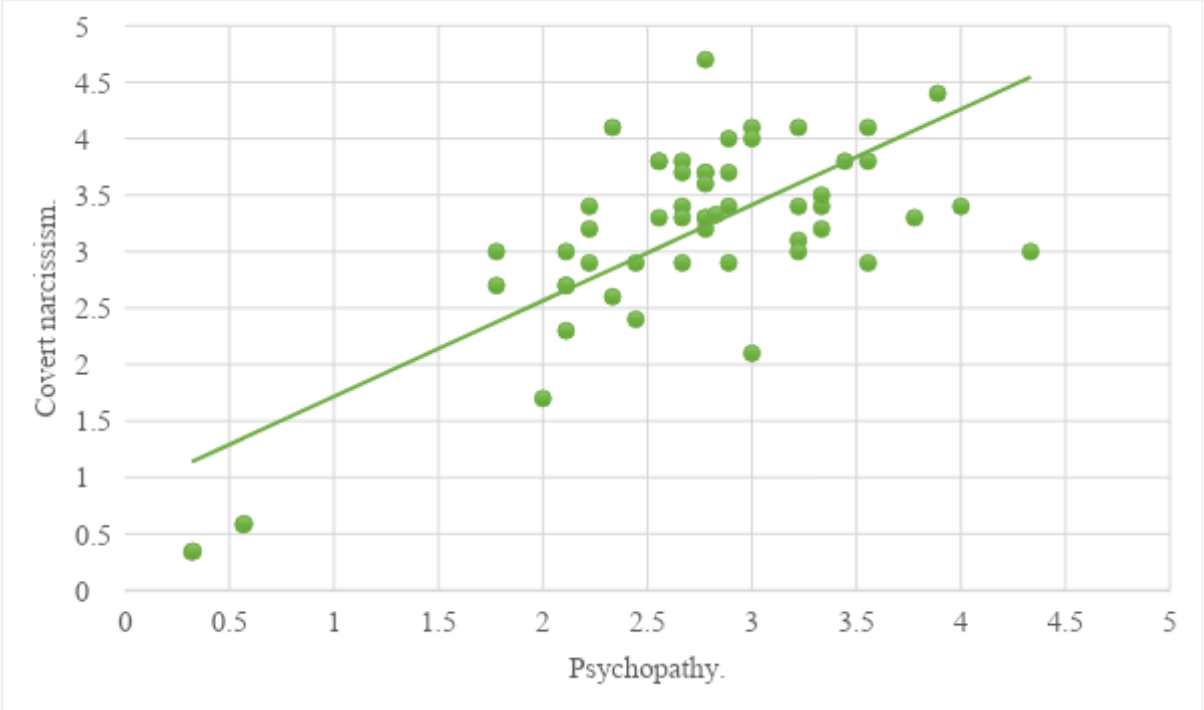

Figure 2. Correlation between Psychopathy and Covert Narcissism. Scatter plot showing quoted ratings by participant for Psychopathy and Covert Narcissism taken from the online survey. Line of best fit shows a moderate correlation.

Discussion

Overall, the correlations between all factors of the Dark Triad and ego-dystonicity were weak to moderate. However, Psychopathy particularly stands out in its relationship to both factors of ego-dystonicity measured. Psychopathic personalities tend to be characterized by guiltlessness and self-centered disinhibition (9). Thus, immoral obsessions (EDQ(a)) resonate with their impulsivity relatively without feeling conscientious. For the implications for the personality sub-category of ego-dystonicity or EDQ(b), the correlation was not as strong because psychopaths tend to think self-righteously. They tend to think that their dominance and actions are "principally correct" because of a lack of remorse or shame and a grandiose sense of self-worth usually present (10).

Since ego-dystonicity and obsession have not been studied in tandem with other personality disorders apart from OCD, these results attempted to explore that uncharted area. Even though two subdimensions of ego-dystonicity were measured, and the results only concretely linked them to subclinical Psychopathy, these results show that there may be hidden relationships between obsessive thoughts and other "repellent" personalities. These findings are also a small step towards understanding the Dark Triad, particularly Psychopathy, as they are often misrepresented and neglected in the mental health community for their socially harmful nature. As Doerfler et al. (2021) reported, higher Dark Triad traits correlate with a weaker sense of self and lower self-concept clarity, particularly secondary Psychopathy and vulnerable

narcissism (8). Furthermore, a few dated studies have shown that the self-concepts of those with high levels of Dark Triad traits are more spontaneous and unstable as they require the utilization of tactics in social situations-manipulation, threatening, etc. (11-12). It is conceivable how ego-dystonicity and non-aligning self-concept relating to ego-dystonicity can contribute to a weaker sense of self. The irrationality of thought seems somewhat consistent with covert narcissism due to its inherent anxious and avoidant nature. The inflated self of narcissists could be explained by factors repugnance or irrationality, but this cannot be concretely stated as these were not formally introduced in our research.

The current study has relative validity and strength. All measurement items used in this study are developed scientifically and often utilized as an aid in diagnosis according to the Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (13). For the EDQ factors, they had acceptable internal validity. The SD3 is relatively reliable, even though some items did not fulfill the goodness of fit (14). Since Siddiqi et al. (2020)'s review of the SD3 concluded that narcissism should be measured holistically and not as a part of SD3 (15), we used two separate tools for narcissism (NGS and HSNS) which are all approved and valid.

Materials and Methods–Procedures and Participants

We surveyed Vietnam in July 2022. The survey's link was distributed through social media platforms (Facebook, Instagram, Twitter, etc., with most platforms targeting Asians). A total of 51 individuals consented to participate in the study. These individuals were members of the community, consisting of 92.2% identifying as Asian, Asian American, Pacific Islander, Desi (AAP) (N=47), 5.9% as both AAPi and Caucasian (N=3), and 1.9% as Caucasian (N=1). Most respondents were aged 16 to 18 (N=35; 68.6%). The remainder of the respondents were either 13 to 15 (N=8; 15.7%), over 18 (N=7; 13.7%), or under 13 (N=1; 2%). As for gender, 30 participants identified as female (58.8%), 12 as male (23,5%), and 9 were either non-binary or did not specify (17.7%).

Measures

Ego-Dystonicity. Purdon et al.'s Ego-Dystonicity Questionnaire, developed in 2007, was used in this study (3). In the survey, we measured 2 out of 4 dimensions in Purdon's original version. The facets measured were (a) "degree of consistency with morals, beliefs, values, and attitudes" or immorality of thought; and (b) "degree of consistency with one's sense of what is rational" or consistency with personality, which will be respectively labeled as EDQ(a) and EDQ(b) in sections below. An 8-item scale for EDQ(a) and a 7-item for EDQ(b) were utilized to measure such factors using a 7-point Likert scale (3). Participants were instructed to rate how much the statements (or items) applied to them on a scale of 1 to 7, with 1 being "strongly disagree" and 7 referring to "strongly agree"; any value between 1 and 7 can be interpreted as applying in certain circumstances or sometimes occurring (3).

The complete EDQ by Purdon et al. consists, as mentioned above, of 4 subdimensions necessary to qualify as obsessional thoughts. They are all slightly different from each other. The

study was able to identify four factors. The factors chosen for our survey were because (a) we felt that morals and personalities are core principles when dealing with subclinical and clinical studies concerning the Dark Triad, and (b) the original 36-item scale was somewhat confusing, especially with language barriers considered. For easier comprehension, the research team provided a brief definition and clarification of each item.

Machiavellianism. Jones and Paulhus's Short Dark Triad (SD3) measure (2014, p. 3) was used (section Machiavellianism). According to Jones and Paulhus (2014), "the key elements of Machiavellianism appear to be (a) manipulativeness, (b) callous affect, and (c) a strategic-calculating orientation." A 9-item scale was used to measure Machiavellianism using a 5-point Likert scale (16). Participants were instructed to indicate how much they agreed with each of the following statements on a scale of 1 to 5: 1 (strongly disagree) and 5 (strongly agree).

Psychopathy. A 9-item scale was used to measure Psychopathy using a 5-point Likert scale (16). Similarly, Jones and Paulhus's SD3 (2014, p. 3) was used (section Psychopathy). Participants were instructed to indicate how much they agreed with each of the following statements on a scale of 1 to 5: 1 (strongly disagree) and 5 (strongly agree).

Grandiose Narcissism. We used the Narcissistic Grandiosity Scale (NGS) by Rosenthal et al., developed in 2020, to measure Grandiose Narcissism (18). Two types of narcissism were measured. Grandiose narcissism presents itself as self-entitlement, a sense of superiority, and a need for admiration (17). A 16-item scale was used, with each item being a descriptive adjective that participants can rate how much it describes them using a Likert scale from 1 to 7, 1 being "Not at all" and 7 being "Extremely" (18). Participants were instructed to rate the descriptive words on a scale of 1-7; any value between 1 and 7 can be interpreted as applicable in certain circumstances or sometimes occurring. Additionally, the research team provided definitions of the words in consideration of language barriers.

Covert Narcissism. Covert narcissism is characterized by entitlement and an anxious and avoidant nature (17). For Covert Narcissism, the Hypersensitive Narcissism Scale (HSNS) by Hendin and Cheek (2013) was used in our study. The section was ten items long with a Likert-like measurement. Participants were instructed to answer the statements by deciding to what extent each item is characteristic of their feelings and behavior, with 1 = very uncharacteristic or untrue to 5 = very characteristic or true, strongly agree (19).

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The Mystery of Peto's Paradox By Jihyun (Olivia) Lim

Abstract

The mystery of Peto's paradox has perplexed evolutionary biologists for many years. The epidemiologist Richard Peto observed that while animals with larger bodies have more cells and therefore a higher likelihood of genetic mutation, they do not have a higher incidence of cancer. Identifying how larger animals have evolved to suppress cancer may help to resolve this apparent paradox. One hypothesis suggests that larger animals have evolved stronger cancer prevention systems, such as improved DNA repair mechanisms, increased sensitivity to apoptosis, or stronger defenses against uncontrolled cell division. Understanding how larger animals have evolved to resist cancer may help researchers identify new methods of cancer prevention and treatment in humans and animals. This review provides an overview of Peto's paradox and the development of cancer suppression mechanisms in large-bodied animals. We explore recent developments in understanding how larger animals have evolved to suppress cancer, including results from comparative and genomic studies. We also highlight new methods for fighting cancer that take advantage of the synergy between cancer prevention pathways.

Keywords: Peto's Paradox, metabolism, hallmarks of cancer, oncogenes, tumor-suppressor genes, apoptosis, somatic mutation, Klieber's Law, reactive oxygen species

Introduction

Cancer results from uncontrollable cell division leading to disease in many organs. Cancer arises from genetic and epigenetic changes, often affecting pro-tumorigenic oncogenes and anti-tumorigenic tumor suppressor genes (1,2). The development and progression of cancer are characterized by a series of hallmark traits common to nearly all cancer types. These hallmarks include uncontrolled proliferation, evasion of growth suppressors, resistance to cell death, and angiogenesis (3,4). The purpose of this paper is to review the concept of Peto's Paradox, examine the molecular mechanisms by which oncogenes and tumor suppressors regulate proliferation, and explore the evidence for a link between cancer incidence and body size across different species (5). We will also explore the relationship between metabolism and cancer, emphasizing how metabolic adaptations or diet may help to explain Peto's paradox.

Background on Peto's Paradox

Peto's Paradox is an evolutionary conundrum that has long perplexed scientists and sparked a heated debate about the evolution of anticancer processes. The impact of natural selection on large body size, cancer susceptibility, and extended longevity is at the heart of Peto's Paradox. Investigating Peto's Paradox may thus significantly contribute to our understanding of anticancer mechanisms that could potentially be exploited for medical applications.

In 1977, Richard Peto discovered that a longer duration of exposure to the carcinogen benzopyrene was correlated to an increased likelihood of cancer progression. He later added body mass to the equation when he asked why humans have a relatively lower risk of cancer compared to mice despite having more cells and longer life spans. Furthermore, he noted that despite the higher theoretical hazards, cancer was not a prominent cause of mortality among many large and long-lived wild animals (5).

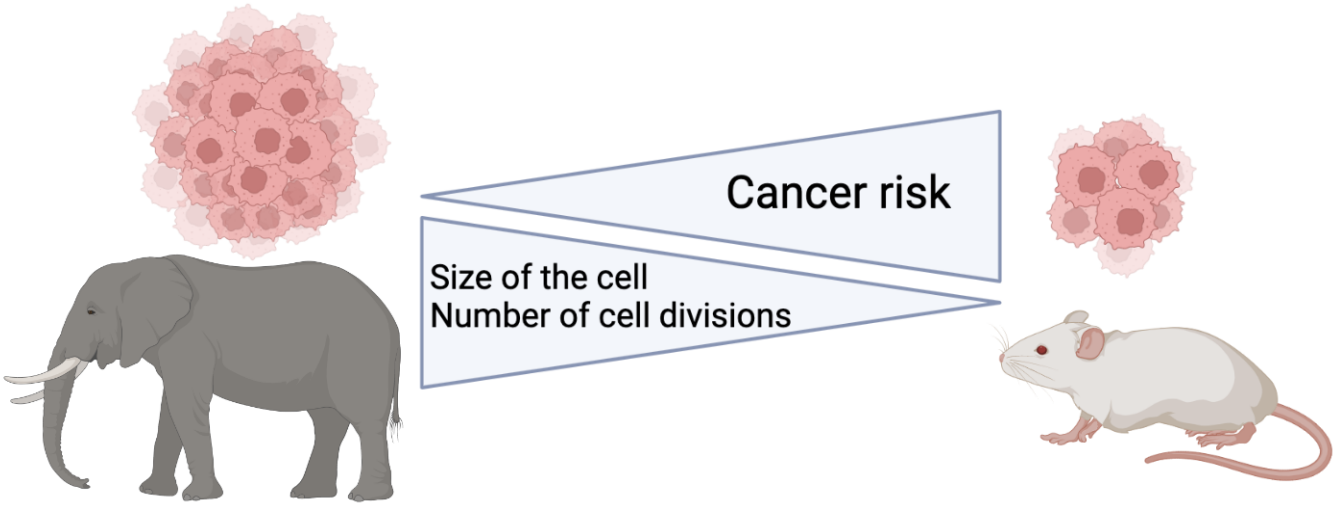
Many cells in a multicellular creature go through a cell cycle that includes division and growth. Every time a human cell divides, it must copy its six billion base pairs of DNA, and mistakes are unavoidable. These errors are known as somatic mutations. The difficulty of controlling somatic mutation increases in animals with larger bodies and longer lifespans. Cancer develops through the accumulation of mutations. Assuming that all proliferating cells have comparable likelihoods of acquiring mutations, each proliferating cell should be at an equal risk of malignant transformation. As a result, if an organism has more cells and more chances to form a tumor, the likelihood of developing cancer should rise. Similarly, if an organism lives for a longer period, its cells have more opportunities to collect mutations. Because the likelihood of carcinogenesis increases with age, an organism's lifetime risk of cancer should similarly increase with age. It is well understood that larger species have longer lifespans, which exacerbates the problem.

However, there appears to be no association between body size, longevity, and cancer among species— a conundrum that is referred to as Peto's Paradox (Figure 1). Peto's Paradox questions how natural selection has transformed the biology of huge, long-lived species to achieve this scaling. Cancer rates vary only about two-fold between multicellular animals, although the size variation between mammals can be on the order of a million-fold (5). Natural selection influences species' life histories and should reduce the risk of cancer during an organism's projected period of fertility. As a result, given an organism's age, it is expected that cancer rates would be similar across species. For instance, laboratory rats and humans differ in lifespan by a factor of 40 and size by three orders of magnitude. Nevertheless, around 30% of both mice and humans are estimated to develop cancer (5). One possible explanation for Peto's Paradox is that giant, long-lived animals are more resistant to carcinogenesis than smaller, short-lived species; however, it remains unknown how larger species achieve this resistance (5).

Fig 1: Two triangles represent the cancer risk and the number of cell divisions associated with animal size. The elephant is a large animal going through many cell divisions while a mouse undergoes relatively less number of divisions with a smaller cell size.

Oncogenic Mutations

Tumor suppressors help maintain homeostasis and act as safeguards against uncontrolled growth, which is one of the hallmarks of cancer. As critical defenders of genomic integrity and cellular regulation, tumor suppressor genes (TSG) exert tight control over cellular processes including cell cycle progression, DNA repair, and apoptosis (6,7). They act to limit tumor development and progression by monitoring and inhibiting uncontrolled cellular proliferation,



underscoring their importance as regulators of cell proliferation and oncogenic potentials. Thus, tumor suppressors are commonly mutated in cancer, thereby allowing cancer cells to acquire the hallmarks of cancer. There are typically two copies of every tumor suppressor, and both of them must be lost or mutated to alter the function of the tumor suppressor (6,7). As somatic cells actively divide, they can experience mutations during DNA replication or as a result of exogenous damage. More cell divisions create a higher potential of mutations in the cells that lead to tumorigenesis. Some examples of important tumor suppressor genes are *TP53* (encoding p53) and *BRCA1* (BRCA1) (7). The impact of tumor suppressors to enhance cancer resistance could explain Peto's Paradox. An experiment to test the hypothesis might be to use genomic analysis to count the orthologs of known cancer genes in different species to quantify the copy number of cancer-associated genes. Functional investigations into the activity of tumor suppressors across species would complement sequencing information. Ultimately, understanding the complex processes governing tumor suppressor activity is critical for understanding the molecular foundation of oncogenesis and employing appropriate treatment approaches.

TP53 gene mutations have the greatest prevalence in human cancer. It encodes the p53 protein to regulate the cellular responses to DNA damage. p53 protein functions as a transcription factor to control gene expressions (6). The important cellular processes controlled by p53 target genes include cell division, DNA damage sensing, and repair, control of cell death, metabolism, and cell migration. Hence these p53 target genes help to suppress cancer by limiting the processes that promote the development of the hallmarks of cancer (7). Different mutations can impair the ability of p53 to suppress tumors. Among 50-60% of homozygous p53 gene mutations occurring in human cancers, about 90% of these mutations cause p53 to lose the ability to suppress cancer, or even gain new functions that promote cancer by encoding missense mutant proteins (7). When germline *TP53* mutations are inherited, they lead to a hereditary disorder known as Li Fraummeni Syndrome (LFS), a disease that increases a person's chances of

acquiring cancer by 90% (6). Soft tissue and bone sarcomas, breast and brain cancer, adrenocortical tumors, and leukemia are among the most common cancers occurring in patients with LFS (6). LFS patients must be screened for cancer frequently beginning in infancy, given the high risk of childhood cancer that persists throughout their lifetimes. Currently, there are no medicines that target the p53 pathway (7).

BRCA1 is a gene that encodes another important tumor suppressor, the BRCA1 protein. BRCA1 aids in the repair of damaged DNA. Natural and medicinal radiation, chromosomal exchanges during cell division, and other environmental exposure can create DNA breaks (8). BRCA1 contributes to the stability of a cell's genetic information by assisting in DNA repair. Additionally, BRCA1 regulates the expression of other genes and plays an important function in embryonic development. BRCA1 interacts with several other proteins, including tumor suppressors and proteins that govern cell division, to suppress cancer (8).

Another crucial tumor suppressor gene is the retinoblastoma protein (Rb) which is often inactivated in cancer. Rb was the first tumor suppressor discovered and is recognized as a negative regulator of cell cycle progression (9). By controlling the activity of the E2F family of transcription factors, Rb regulates numerous cellular functions. While it plays a pivotal role in limiting cell cycle progression for its tumor suppressor function, research has revealed that many protein partners of Rb are engaged in other cellular processes that also contribute to tumor suppression (9). Many of the non-canonical roles attributed to Rb are linked to genomic instability, a cancer hallmark associated with poor prognosis, tumor heterogeneity, and the development of therapeutic resistance. The non-canonical activities of Rb include promoting DNA repair, chromosomal condensation and cohesion, centromere and telomere structure, and transposable element silencing are evident (9). The discovery of these non-canonical roles is essential as they aid in understanding how Rb inactivation leads to tumorigenesis and the development of therapeutics for retinoblastomas and other Rb-deficient tumors (9).

TSG redundancy may inhibit cancer in large animals by preventing cells from acquiring the mutations necessary to establish a malignant phenotype. Accordingly, human cells require more mutations than mouse cells to become immortalized in cell culture. To immortalize human fibroblasts, both the Rb and p53 pathways must be inactivated, but mouse cells only require the p53 pathway to be inactivated. Tumor resistance was increased in mice genetically altered to have additional copies of tumor suppressor genes such as *Trp53 or Cdkn2A*. Interestingly, the current elephant genome build (*Loxodonta africana*, Ensembl release 59) contains 12 orthologs of the human gene *TP53*, as well as one copy of each of the genes encoding the p53-family members p73 and p63. Each of these genes (*TP53, TP63, and TP73*) is found only once in the human genome (7). The increased number of copies of tumor suppressors may explain how elephants may have such huge bodies and live such long lives (up to 70 years in the wild) while not succumbing to cancer at a higher frequency than smaller animals. Alternatively, larger animals might have fewer copies of proto-oncogenes (3). Having fewer proto-oncogenes would lower the likelihood of an oncogenic mutation occurring, and thus lower the overall risk of oncogenesis. Indeed research suggests that mice lacking the proto-oncogene *Hras1* grow fewer

papillomas than wild-type mice (3). Genomes with fewer copies of proto-oncogenes would be less vulnerable to cancerous mutations that could generate the phenotypes required for cancer. Needless to say, proto-oncogenes have other tasks, so eliminating them could be harmful in other ways. Many tumor suppressor genes have a tissue-specific expression (6). Cells of larger species may have developed expression patterns in which more TSGs are expressed in any single cell than in smaller, shorter-lived animals, even if the genome contains the same number of TSGs (7). According to this concept, large animal genomes may contain more TSGs that are more widely expressed than smaller species.

The Hallmarks of Cancer and Their Role in Peto's Paradox

There are more than eight main hallmarks of cancer that grant cancer cells a selective growth advantage over healthy cells. Some of these hallmarks include angiogenesis, insensitivity to growth inhibition, resistance to apoptosis, invasion and migration, sustained proliferation, replicative immorality, changes in metabolism, and evasion of the immune system (3).

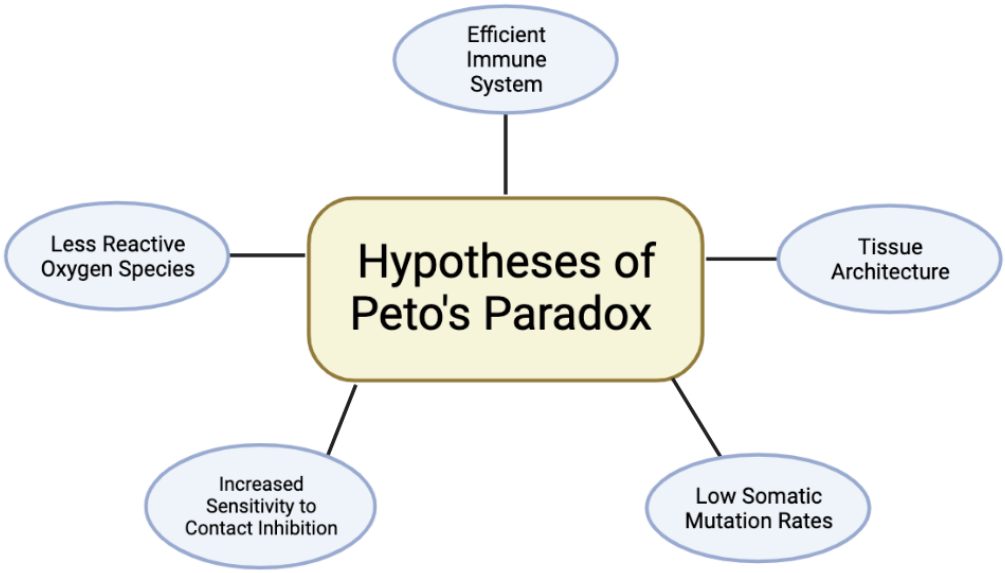


Fig 2: Five different hypotheses to support Peto's Paradox illustrated in circles

Evasion of the immune system is a critical hallmark of cancer. As tumor cells develop, they evolve mechanisms to avoid elimination by the immune system (10). Differences in immune surveillance may explain discrepancies in cancer resistance between species. In mice treated with carcinogens, the growth of tumors that are initially immunogenic is delayed due to enhanced immune system surveillance (11). However, as the tumor co-evolves with the immune system, unsuspected tumor variations are selected, giving rise to the phenomenon of immunoediting (12). Chronic antigenic stress may exhaust the immune system, resulting in poor surveillance, similar to what is observed in chronic viral infections. Large, long-lived creatures may have more effective immune monitoring for neoplastic cells than smaller organisms (12).

Cancer cells avoid the immune system in multiple ways including creating a microenvironment to compete for nutrients and suppress the immune system, signaling immune cells to stop attacking the normal immunosuppression mechanisms (12). Furthermore, when the tumor antigens are exposed for a longer time, cancer cells induce immune exhaustion by making the immune cells ineffective at attacking the tumor (3,12). To turn off the immune responses, immunosuppressive cells such as tumor-associated macrophages and regulatory T cells can be recruited (11). Hence it could be hypothesized that the mechanisms of immune evasion could be circumvented or decreased in larger animals. Larger animals such as the elephant may have a more active immune system that makes it harder to turn off or could have better mechanisms for recognizing the tumors (11). A follow-up investigation to test this hypothesis would be to assess the immunological response to cancer-associated proteins in different species.

Another hallmark of cancer that relates to Peto's Paradox is a change in tissue architecture that may affect the frequency of metastasis or the spread of tumor cells to new sites in the body. Metastasis is controlled by tissue architecture, cell compartmentalization, and cell motility dynamics (13). Many tissues, such as the crypts of the intestines, are made up of tiny proliferative units containing multipotent stem cells and progenitor cells (11). The hierarchical structure of tissues from undifferentiated stem cells to differentiated daughter cells has been postulated as an important aspect of cancer development (13). As differentiating cells are evolutionary dead-ends, the effective population size of a somatic tissue is likely to be determined mostly by the number and dynamics of stem cells. However, a mutation that interrupts differentiation in a non-stem cell may also result in a cancerous cell lineage by causing dedifferentiation of the cell into a more 'stemlike' state (11,13). By simply adding non-stem phases to a "serial differentiation" model, it is possible to increase the number of cells and the rate of cell turnover without increasing the number or proliferative activity of somatic stem cells (12,13). Changing the number of stem cells, crypt density, or differentiation and division dynamics could improve the tissue's ability to resist malignant transformation.

Signals from the microenvironment can also decrease 'selfish' cellular proliferation (11). Cell contact inhibition, for example, differs between human, mouse, and naked mole-rat (*Heterocephalus glaber*) cells. Due to the early activation of the p16 pathway, which leads to hypersensitivity to contact inhibition, naked mole-rat cells cease dividing at considerably lower densities in culture than human and mouse cells (3,11). Although naked mole rats and mice are both small species, naked mole rats live substantially longer (28 years) than mice (4 years). Cancer was not found in any of the 250 necropsies performed on dead naked mole rats in captivity (2,10). Although only observed in vitro, hypersensitivity to contact inhibition may have developed to suppress cancer and allow the naked mole rat to live longer (10). Similarly, early cell senescence signals could be activated in huge, long-lived organisms to stop unchecked growth.

If larger animals have lower somatic mutation rates per cell generation, more cell divisions would be required for a cell to acquire the essential mutations to become malignant (12). The mutation rate is determined by the error rate of DNA replication and the rate at which

errors are fixed (2,12). This could be accomplished via a variety of strategies, including improved DNA damage detection and repair systems. Experimental findings, on the other hand, show that mice and humans have comparable mutation rates (11,13). However, the hypothesis that larger animals have lower somatic mutation rates could be tested by measuring and quantifying somatic mutation in vivo in different species.

Cells' susceptibility to programmed cell death, known as apoptosis, may differ between large and small creatures. Cells from huge bodies may be more vulnerable to DNA damage or the activation of oncogenes, making them more prone to apoptosis (14). Observations of human and mouse cell cultures lend support to this notion. When human cells are irradiated, many die as a result of apoptosis caused by DNA damage. Despite the extensive DNA damage caused by the radiation, a higher percentage of mouse cells survive and continue to divide (14). Apoptosis caused by DNA damage removes the injured cell from the population rather than fixing the DNA and potentially propagating residual mutations in the tissue (11,14). However, there is likely to be a trade-off between apoptosis preventing cancer and generating senescence as a side effect.

Changes in Metabolism

Metabolism is present when foods are converted into energy and raw materials with the help of cells for growth or repair. The ultimate purpose of metabolism is ATP production which releases the primary energy source used for cell division and growth (12). Not only entailing a breakdown of macromolecules of catabolism, but metabolism also plays a crucial role in the development and progression of cancer. As cancer cells go through metabolic changes, they adapt to the unique challenges of the tumor microenvironment (15).

Cancer cells undergo profound metabolic changes, allowing them to adapt to the unique challenges of the tumor microenvironment. The shift toward aerobic glycolysis, known as the Warburg Effect, is one of the most well-characterized changes (12, 15). The Warburg Effect occurs when cells preferentially use the anaerobic glycolysis pathway to produce energy from glucose, even in the presence of oxygen, rather than the more efficient oxidative phosphorylation process. This metabolic shift allows cancer cells to produce more of the building blocks required for cell growth and division (15). Alterations in lipid, amino acid, and nucleotide metabolism are among the many metabolic changes commonly observed in cancer cells (10, 15). These changes may allow cancer cells to adapt to the limited nutrients and oxygen often found in the tumor microenvironment, allowing them to survive and proliferate despite hostile conditions. The link between metabolism and cancer is intricate and multifaceted (15). While metabolic changes can help cancer cells survive and grow, they can also make cancer cells vulnerable to metabolic inhibition. This has resulted in the development of a new class of cancer therapeutics that target cancer cells' metabolic vulnerabilities.

If reactive oxygen species can cause carcinogenesis, then the pace of metabolism may correlate with the rate of cancer in animals of various sizes (18). A comprehensive assessment of marine mammal cancers referenced studies with very large numbers of necropsies, and the findings indicate that whales had considerably lower cancer rates than smaller mammals like the

sea lion (19). An examination of a global database of over 15,000 wild or captured elephants tends to confirm Peto's Paradox. Of the 616 dead elephants in the experiment, 18 (approximately 3%) have been linked to cancer; however, these figures do not offer a lifetime cancer rate (19). Nonetheless, these results suggest that elephants do not frequently die from cancer, compared to 12.5% of human deaths from all types of cancer. (18). Natural mouse fatalities with aging have been reported for over 2000 mice, with approximately half succumbing to cancer by 800 days of age (18). These data appear to corroborate but do not prove Peto's Paradox's broad contention.

Klieber's Law

One explanation for Peto's Paradox relates to differences in metabolic rate between species. The relationship between animal body mass and the amount of heat production per day has been recognized for many decades, beginning with the observations of Max Klieber in the 1930s. Klieber discovered that body mass correlates with ¾ the power of the whole body basal metabolic rate (B= M $\frac{3}{4}$; where M is body mass) (16). The exact magnitude of Klieber's law, such as $\frac{2}{3}$versus $\frac{3}{4}$, has been a source of contention. The basal metabolic rate is related to heat loss through body surface area, which is more directly related to the $\frac{2}{3}$ power (16). A updated review of existing data reveals that the power function is closer to $\frac{3}{4}$ than $\frac{2}{3}$, while there is significant variations across mammalian subgroups (11,16). It is worth noting that the mass-specific metabolic rate B' is defined as B/M and reflects metabolic rates normalized to tissue mass, such that B' = M$\frac{1}{4}$: the slope equals the exponent when plotted as logB' versus logM (17). From a biological standpoint, this power function is visible in mice's substantially greater metabolic rates, which implies orders of magnitude higher than that of elephants. These differences in metabolic rate could account for Peto's Paradox.

West, Brown, and Enquist (WBE) proposed a theoretical explanation for the $\frac{3}{4}$ power law function, focusing on nutrition supply through the geometry of the circulatory system (16, 17). In essence, a theoretical model of the circulatory system was studied that resembled a fractal network branching down to the end capillaries. If the branching pattern is replicated from the aorta to the capillaries, the end capillary density in this model would predict the rate of nutrient perfusion to cells, which controls the metabolic rate. According to this hypothesis, the larger the animal, the sparser the capillary density in tissues (17). The increased inter-capillary distance is considered to result in lower nutrition delivery and a steeper oxygen gradient from blood vessels, resulting in decreased respiration and oxidative phosphorylation and, ultimately, decreased specific metabolic rates (17).

Nagy et al. offered a different idea of Peto's conundrum regarding the formation of hyper tumors. Within a natural selection, tumors may favor cheater cells that use vasculature created by angiogenic cells. These cheaters have the potential to expand and parasitize the original tumor. The hyper-tumor would lower the tumor's overall fitness and may even lead it to retreat (11). According to Nagy et al, deadly tumors must be significantly bigger in larger animals, providing

the hyper tumor more time to grow and forcing the parent tumor to necrotize (11, 21). This model predicts that big animals would frequently carry macroscopic tumors that will be proportionally more necrotic than tumors in smaller creatures (21). As a result, increased necrosis in the larger tumors of large-bodied animals could limit tumor growth and reduce the likelihood of cancer mortality (11, 21). However, the hypothesis is not empirically proven in laboratory conditions. Additionally, it is difficult to experimentally compare the fitness of different cell populations in a tumor, making this model difficult to test.

Reactive oxygen species (ROS) are produced by redox reactions involving the movement of electrons. ROS are generated in two ways: from endogenous sources inside the body, such as oxidative mitochondrial metabolism; and from exogenous sources arising from external factors such as ultraviolet radiation. Intracellular ROS impact cellular damage, oncogenic transformation, genome instability, hyperproliferation, immortalization, angiogenesis, and more (18). While moderate ROS levels are required for normal cellular functions, an increased metabolic rate or mutations in certain cancer-associated genes may elevate the ROS production in tumor cells (18, 19). Hence relatively higher metabolic rates in small animals compared to their body mass would lead to more production of ROS from the mitochondria (19). This might consequently result in more mutations in DNA and thus a higher likelihood of cancer risk, which supports Peto's Paradox.

However, in 2021, a study collected a large dataset from 'Species360' and 'Zoological Information Management System' which is an international non-profit organization to test Peto's Paradox computationally. These collected zoo animals involve a variety of species under human supervision with regrouped information from 1,200 zoos worldwide. When examining living organisms within distinct taxonomical classifications such as primates, carnivores, Rodentia, artiodactyls, and Chiroptera, it becomes evident that carnivores exhibit a relatively higher risk of cancer development (20). This observation suggests that the consumption of meat and the dietary habits of carnivores entail a heightened susceptibility to oncogene activation (20). One plausible explanation supporting this hypothesis is that a diet rich in fats and low in fiber represents a significant contributing factor to cancer incidence among carnivores (20). Moreover, carnivores predominantly occupy the highest trophic level, thus implying increased exposure to bioaccumulated carcinogenic compounds, including pollutants (20). Notably, the consumption of raw meats by carnivores further intensifies their exposure to pathogens, which exacerbates the oncogenic transformation (20). Consequently, the increased mortality risk resulting from cancer incidence primarily affects carnivores, specifically due to their unique metabolic characteristics.

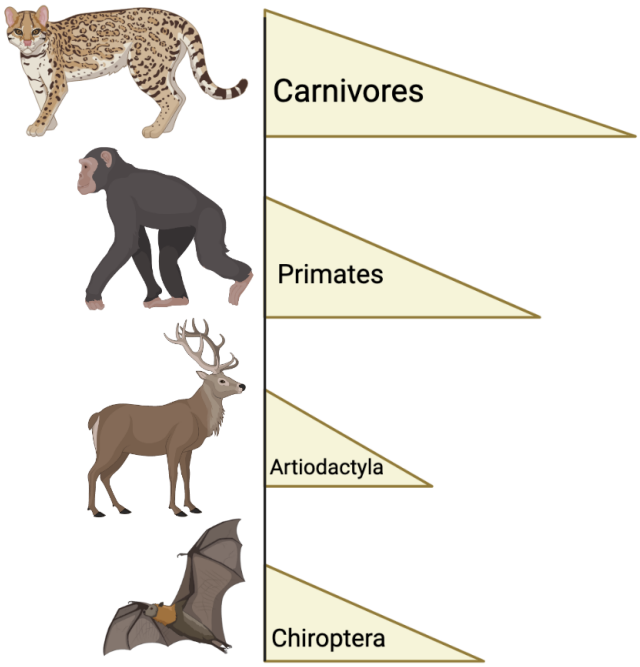


Fig 3: Different sizes of triangles show the comparative degree of cancer mortality risk associated with various taxonomy of species

Conclusion

This review paper discussed the hypotheses that underpin Peto's Paradox as it relates to the comparative relationships among different species of animals like the mouse and an elephant. Presently, there exists limited data to substantiate this hypothesis. However, a database study investigating the correlation between a carnivorous diet and cancer risk provides empirical evidence that supports this paradox. Peto's Paradox is an important mechanism to gain a comprehensive understanding of the fundamental hallmarks of all types of cancer. Although Peto's Paradox primarily focuses on the multispecies of animals, a better understanding will lead to valuable insights into human cancer. Consequently, a refined understanding of cancer will facilitate enhanced cancer treatments for humans.

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Authors

Jihyun Lim, the author of this article, is a rising 12th grade at the Chadwick International School, Incheon, South Korea. Her passion for life sciences and biology field has motivated her to write this review paper about Peto’s Paradox with the help of Amy Tarangelo.

Psychological Theories Describing How the Media Can Help Influence People's Beliefs and Perceptions on Political Issues By Binghui Sun

Abstract

The agenda-setting and framing analysis theories are essential theoretical frameworks in media studies. The agenda-setting theory suggests that the media can influence the public agenda by emphasizing specific issues and topics. In contrast, the Framing analysis theory suggests that the media uses specific techniques, like employing certain word choices or highlighting particular statistics, to shape how we interpret and understand certain issues. Both theories emphasize the power of media to shape public opinion and behavior. By talking about different psychological theories, I discuss how the media can help influence people's beliefs and perceptions on political issues in this essay. This topic is important to me because I study IB psychology in my high school, and I feel very passionate about using psychology knowledge to discuss a social issue. I also want to practice the ability to think critically while being rational.
Key Words: Psychological theory describing media influence, agenda setting theory, priming, framing analysis theory, emotional framing, narrative framing

Introduction

The agenda-setting and framing analysis theories are essential theoretical frameworks in media studies. The agenda-setting theory suggests that the media can influence the public agenda by emphasizing specific issues and topics. In contrast, the Framing analysis theory suggests that the media uses specific techniques, like employing certain word choices or highlighting particular statistics, to shape how we interpret and understand certain issues. Both theories emphasize the power of media to shape public opinion and behavior.

Agenda Setting Theory

Under the Agenda-setting theory, the media can shape public opinion and perceptions by emphasizing specific topics and downplaying others. Through this process, the media can create a "hierarchy of attention" among the public. This theory by Maxwell McCombs and Donald Shaw in their 1968 study showed that the topics chosen by the media were more likely to be the ones people chose to discuss (Frederick & Evan,2021, p.16). While agenda setting primarily refers to media power, it can also apply to other institutions, such as the government and the public.

Priming

Priming in agenda-setting theory is a phenomenon that occurs when media outlets prioritize the coverage of specific political issues over others. Public opinion and public perceptions of various topics are influenced and shaped (Van et al. 30). Priming sought to influence how people think about political issues by highlighting particular topics, leading to a greater emphasis on those topics and leaving other issues in the background. For instance, if

media outlets continuously highlight climate change issues, people might think it is a significant concern, even if other matters are also pressing. Priming may lead to media bias, as the media outlets may be more likely to cover stories that support their political views. Priming can also shape public opinion by reinforcing existing beliefs and opinions about political issues. It can even lead to new opinions and attitudes as people rely on certain messages and ideas they may not have encountered before. Priming may also emphasize certain policy aspects, such as potential costs or rewards, rather than a more holistic view of the issue. By focusing on specific aspects of an issue, the media can shape our perceptions of it and its importance.

Framing

Framing in agenda-setting theory refers to the idea that the media plays an essential role in shaping public opinion and directing attention to specific topics. The media can draw attention to certain aspects of a political issue while de-emphasizing or ignoring other aspects. A biased or incomplete understanding of the issue can develop, influencing people's political beliefs and perceptions (Huma Parveen,2017, p.6). For example, in the debate over healthcare, if media outlets frame the discussion around costs to taxpayers, it can lead to a more negative public view. In contrast, framing it around health benefits or lives saved can create a more positive perspective. The media's Framing of political issues can thus lead to a framing effect, which defines the influence of Framing on the interpretation of messages and the subsequent judgment and behavior of receivers. This framing effect can manipulate public opinion and lead people to believe certain things about an issue while ignoring other aspects. Additionally, Framing can reinforce existing beliefs and opinions, leading people to view issues in a certain way and accept particular views as truth. Forming inaccurate and misguided opinions can be dangerous.

Framing Analysis Theory

Framing analysis theory explores how different media aspects can shape people's views and interpretations of events and stories. It focuses on information presentation and how it can influence opinions and beliefs (Tewksbury et al.,2019, p.40). Moreover, it explores how information appears, such as highlighted and omitted, and how language can affect how readers interpret its stories. For example, a news story about a violent protest may highlight the destruction caused, which could result in readers perceiving the protesters as aggressive or lawless. However, if the same event is framed around the protestors' cause or the police's reaction, it might elicit sympathy for the protestors. This type of Framing could lead to different interpretations from readers.

Emotional Framing

Emotional Framing is a communication strategy that attempts to shape how individuals interpret political issues and form opinions by using emotionally charged language, images, and symbols. It seeks to elicit an emotional response from the audience. It highlights an issue's positive or negative aspects, allowing for selective emphasis on specific facts or values. Framing

focuses on the emotional aspects of an issue to elicit a response from the audience rather than on facts used to evoke a response (Huma Parveen,2017, p.9). For example, a politician might describe the struggles of a middle-class family during an economic recession, causing the audience to feel sympathy or anger and thus garner support for their economic policies. Emotional Framing can shape political beliefs and perceptions by evoking certain emotions in the audience. It can frame an issue to make an idea more attractive or less desirable or make one set of beliefs or policies appear more legitimate than another (Amsalem et al.,2022, p.400). Thus, Emotional Framing can influence how people perceive political issues, which can make communication more effective because it can create an emotional connection between the audience and the issue or policy, making the message more memorable and impactful.

Narrative Framing

Narrative framing theory seeks to understand how facts, stories, and opinions influence our beliefs and perceptions about political issues. Framing theory examines how language shapes conversations, evokes emotion, and influences decision-making and policy preferences (Amsalem et al.,2022, p.400). Narrative Framing influences public opinion by emphasizing certain aspects and minimizing others.

In recent years, narrative Framing has been used significantly in political campaigns and media. For example, in the 2020 US presidential election, both candidates used narrative Framing to discuss immigration, healthcare, and the economy (Pérez-Curiel et al.,2021, p.156). Joe Biden used rhetoric such as "building back better" to emphasize his commitment to improving the economy and "building an immigration system that works" to emphasize his commitment to immigration reform. Meanwhile, Donald Trump used language such as "build the wall" to emphasize his commitment to border security and "make America great again" to emphasize his commitment to restoring American greatness.

Narrative Framing is a powerful tool for influencing public opinion and shaping decision-making. They can present the issue as a narrative, with a protagonist, a conflict, and a resolution (Huma Parveen,2017, p.10). By understanding how language and stories frame conversations and shape our beliefs and perceptions, we can better understand the power of political narratives.

Conclusion

The agenda-setting and framing analysis theories have both been instrumental in helping to shape people's beliefs and perceptions of political issues. Agenda-setting theory focuses on how the media can prioritize specific political issues, thus influencing the public's view of them. Framing analysis theory examines how media frames the discussion of specific political issues, helping to shape public opinion by emphasizing certain aspects of the issue. Together, these theories help shape public opinion and create a better understanding of political issues. By focusing on the aspects of an essential issue and highlighting the aspects relevant to the public,

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Understanding the Role of Museums in Indian Primary and Secondary Education By Falak Shah

Abstract

The role of museums in Indian education, or a lack thereof, seems to have begun with its etymological roots in the East; The Proto-Indo-European root “Men-”, translated to “To think”, with derivatives related to qualities or states of the mind in Eastern philosophy, lead to a theoretical rather than a physical manifestation of the same. The initial conception of knowledge as an abstract, theoretical medium that cannot be confined to a physical space limits the role of material culture in education, a gap that poses a threat to the dissemination and preservation of genuine, relatively unbiased cultural knowledge. This paper aims to examine the general implications of the study of material culture in Indian education, the decolonization of historical knowledge, national state funding for museums, and the ethics of repatriation, relying primarily on secondary literature reviews as the basis for these analyses. Upon reviewing museum visitor statistics, the results showed a clear disconnect between students and museum learning in India, even when adequate state funding was provided. To contextualise these findings, this paper delineates the role of museums in global education systems, providing evidence for the benefits of the incorporation of the same in the equivalent Indian systems.

Keywords: *Museums; Indian Museum Education; Decolonization; Repatriation of Indian artefacts*

Introduction:

Defined as “Buildings in which objects of historical, scientific, artistic, or cultural interest are stored and exhibited,” (Oxford) modern museums have a rich history of cultural education in the West. Derived from the Ancient Greek term "Mouseion," translated to "Seat of the muses," Panhellenic sanctuaries, temples of the muses, temples of Athena, and libraries were the first real museum-like structures, with the Latin translation "Places of philosophical discussion." Revered as places of knowledge, by the 15th century, the term was revived to describe Lorenzo de Medici’s collection of art, statues, manuscripts, and antiques in Florence, later donated by the Grimaldi brothers to be displayed for the public of Venice in the early 16th century. It wasn’t, however, until the 17th century that the museum in its current form became a part of education, and by the 17th century, "Museums" represented collections of oddities with the first official museum housed at Oxford University: The Ashmolean. While India has a storied history of the *chitrasala* (Sanskrit, translated to. “Picture gallery”), the country followed a similar trajectory for its first public museum - Sir William Jones of the East India Company, one of the first British historians, formed the Asiatic Society of Calcutta to study and disseminate the cultural tapestry of India’s wealth of textiles, artefacts, and art from trade with the British, Persian, Armenian, French, Portuguese, and Danish sailors. Approved in 1796, the "Imperial Museum" (now the

"Indian Museum") of Calcutta was the first formal museum of India and since then, every major city in the country has a historical museum of some sort (Biswas, 2009).

Even though India's history of post-colonial education suggests a logical, almost organic assimilation of museums in modern education, the lack of material culture in education seems to have begun with its etymological roots in the East; The Proto-Indo-European root "Men-", translating to "To think," with derivatives related to qualities or states of the mind and/or thought in Eastern philosophy lead to a theoretical rather than a physical manifestation of the same. While this may not seem like much of a problem, the initial conception of knowledge as an abstract, theoretical medium that cannot be confined to a physical space limits the role of material culture in unbiased education, an issue that when coupled with the lack of funding for archaeology in India poses a threat to the dissemination of genuine, hereditary cultural knowledge, and its preservation in turn. This gap has, however, been recognised, and museums have been receiving more funding, with a projected Rs. 227 crore ($27559275) allocated to their development between 2021 and 2056 as per the Ministry of Culture's museum grant scheme; there is no shortage of museums in India. With the example of the city of Mumbai, the financial capital of India, there are several well-funded history, natural history, art and science museums, but they have no real role in formal education yet (Chaturvedi, 2022). This commentary will focus initially on the role of museums in the three national boards of Indian education, the CBSE, CISCE, and NIOS, before exploring international boards such as the IGCSE and the IB in Indian schools.

While museums in their current state, as well as Indian systems of education are inherently colonial, it is essential to understand the systemic biases of historical knowledge before attempting to reclaim India's postcolonial narrative. While seemingly meaningless, an exemplary instance of the problem at hand can be observed simply by analysing the countless names for the Revolt of 1857: British historians refer to it almost exclusively as a "mutiny", or a "rebellion", while Indian historians classify it as a "revolt," "insurrection," and even "the First War of Independence." In terms of the archaeology of knowledge (Foucault, 1969) and the subsequent discourse on language, these seemingly meaningless semantics hold the power to mould the exact manner in which knowledge is perceived as outlined by the Conceptual Model of Learning (Falk and Dierking, 1992), especially when displayed in a socially credible setting such as a museum. When this portrayal of the British as righteous saviours of sorts crosses over into museums from education, it effectively cements their role in history as the victims of an aggressive act while ignoring centuries of ethical and political complexities, essentially eliminating the role of nuance as a historical moderator. *The Nehru Report* (1928), for instance, was censored before being placed in the Victoria and Albert Museum, London, removing sentences that explicitly confronted British aggression in India. Simply manipulating a text can change its connotation completely, affecting its dissemination, and therefore, perpetrating cycles of systemic biases for centuries to come It is almost impossible to detangle colonial influences from Indian history as it is studied today, but museums in India can be instrumental in this process; this does, however, raise the issue of repatriation. The astounding lack of repatriation in

the twenty-first century is evident based on the fact that 2022, 75 years after India's independence, was the first time a museum in the United Kingdom, the Glasgow Life Museum, ever returned "stolen artefacts" to India.

The present research paper aims to understand the role of traditional museums in modern Indian education systems by examining their general role in education, their current role in national education, and discussing their educational outreach initiatives, as well as the general implications of the study of material culture in the Indian context.

Discussion–Theme I Museums in Primary and Secondary Education: A Global Overview:

Most primary and secondary schools plan at least one annual field trip to either a history, art, or science museum for educational purposes (Hein, 1998). Museum educators often have to defend their relevance in the modern world, and in addition to the obvious academic value of museums, the environment requires significant social development to function within (Stevenson, 2017); As they familiarise themselves with a new environment while absorbing unique information, students find themselves responsible for their own informal learning, often developing lifelong interests in the process based on what they gravitate towards. Having combined visual and auditory sources of information, students begin to develop more nuanced, well-considered arguments in their daily lives as their cognitive processing improves (Paivio, 1991). They can also serve as records of current history to keep future citizens better informed. Museum curator and educator Maria Vlachou stated "I don't see museums as islands, I cannot conceive cultural institutions remaining untouched by what is going on around them," and reaffirming this narrative helps frame museums in a far more relevant context to modern education for the same reasons it is important to study history: An understanding of the general past, context for the present socio-political and economic state of the world, critical thinking and research skill development, and the formation of nuanced, well-considered, and thorough arguments.

According to the International Council of Museums, the reason for the exclusion of museums from traditional curricula is that its present definition does not include the terms "education" or "cultural interaction" (ICM). Following the rise of anarchist education and deschooling in the twentieth century, however, the establishment of several alternative educational institutes has led to more space for curriculum changes that shape the way information is communicated and applied based on the demands of the modern world. Alternative educational pedagogies such as the Waldorf and Montessori schools focus on five key aims, as outlined by Ron Miller: Respect for the person, balance, decentralisation of authority, noninterference among the political, economic, and cultural spheres of society, and a holistic worldview. These ideological guidelines have made them essential examples for the role of museums in current global education, as they place considerable emphasis on experiential and naturalistic learning, a philosophy that extends to museums.

With reference to Kailey Kallio's 'Critical Outcomes of Museum Learning,' which states that "cognitive theories and constructivism have been ruling pedagogical thinking just as much

in schools as in museums," (Kallio, 2015) defines museums as places of dynamic knowledge that can be processed actively, unlike cultural institutions such as theatres or cinema houses. With the highest number of art, history, and science museums in the world (a total of 33,098 as of March 2023; Arna Bontemps Museum, 2023), the United States of America spends more than 2 billion dollars a year on museum-based educational activities for K-12 education in association with the American Alliance of Museums (AAM). The AAM predicts that the next decade of education will be defined by "self-directed, experiential, social and distributed learning designed to foster 21st-century skills of critical thinking, synthesis of information, innovation, creativity, teamwork and collaboration," a revolution they believe will be structured around museums. Their three key initiatives include: fostering a national dialogue about museums in education, launching a micro-website that allows students and educators to submit their perspectives regarding the same by 2025, and digital badging, or micro-credentialing, which grants credits for different forms of museum learning. These initiatives, in conjunction with the six 'Magnetic Museums,' have helped refocus the conversation to consider a balance of educational pedagogies, cultural philosophies, stakeholder benefits, and accessibility. Additionally, museums such as the Metropolitan Museum of Art, the Smithsonian, and the Chicago Field Museum offer credible high school internship programmes to legitimise the role of museums in experiential learning, skill building, and work experience for students interested in history, anthropology, archaeology, museology, art history, and/or education.

In Singapore, where history museums are valued as places of investigation and analysis in an educational capacity, science museums are seen as places of inquiry and experimentation. Working to make this area of knowledge relevant to modern scientific education, the Science Centre Singapore aims to "make science accessible and engaging, creating an environment where Singaporeans are empowered to advance their own learning and, hopefully, are inspired to do something incredible with their futures" (Science Centre Singapore, 2023). Through a range of interactive installations, school-specific programmes to supplement their respective science curricula, scientific magazines and natural history guidebooks, they have slowly been revitalising the pivotal role museums play in formal education in collaboration with the Ministry of Science and Technology. With over 1 million visitors annually, they have succeeded in updating the museum regularly since the 1970s to remain relevant to the acquisition of knowledge; with an institution seemingly entrenched in permanence and antiquity, the dynamic nature of such museums, regardless of the type, is truly admirable. Defining themselves as "A place where science befriends and transforms the minds of millions," (ibid.) the Science Centre has tailored their social value to align with the needs of students and young innovators, cementing their place in modern education.

While the inclusion of experiential learning that is not necessarily vocational in education may seem like a relatively modern concept, Finland has been exploring the same for centuries through intergenerational learning. With 151 professionally managed museums, 3 national museums and over 1000 volunteer-based local museums, Finland has several government agencies dedicated to the maintenance of the same, not only in physical terms, but with reference

to their socio-cultural value as well. Usually controlled by a combination of a few institutions such as the Finnish Heritage Agency, the Finnish Museums Sector, The Finnish Local Heritage Federation, the Association of Cultural Heritage Education, The Finnish Antiquarian Society, the Nordic Association of Conservators, and the Finnish Museum Association, (Finnish Ministry of Education and Culture, 2022), museums are considered an essential part of the economy and the educational system in Finland, bringing over 540 million euros in through visitorship and donations from approximately 7.6 million visitors per year (Finnish Museum Association, 2022).

To discuss the depth of this relationship regardless of the local status or specificity of the museum, the unique example of the Salla Museum of War and Reconstruction, a part of a 2013-2016 'Museums as Media Educators' project provides fascinating insights about the reality of museum learning (ibid). Working with a local seniors' association and a group of local schoolchildren, the museum requested the students to prepare a list of questions to ask the seniors about cooking, hunting, gathering, war, communication, and community. As the students asked the seniors the aforementioned questions at the museum in groups of 2 or 3, they recorded the answers on an iPad and created a fully edited version following their conversation. In addition to this being beneficial to the students to improve their cultural knowledge, social skills, and technological skills, it benefited the seniors in turn as they reconvened at the museum to watch the recordings after being taught how to use modern technology. While this activity seems to undermine the role of the museum itself, it is places like that that can provide a credible and trustworthy environment within which to facilitate open conversation, encourage intergenerational knowledge trades, and contextualise new information for both groups in a mutually beneficial arrangement that can easily be replicated at a local level and focused to specific issues through interactions with professionals in a certain field (ibid).

Upon reviewing specific examples, agencies, and educational pedagogies in different countries, this paper will now explore their generalisability to the Indian context after first outlining the structure of education in India and the current role museums play in the same.

Theme II - The Structure of Education in India and the Present Role of Museums:

The Government of India's Ministry of Education recognises five national boards, further categorised into those under the Department of School Education and Literacy, and those under the Department of Higher Education. This section will focus on primary and secondary education, and while Indian schools do teach a variety of international curricula, this section will focus solely on Indian national boards, both public and private. The Department of School Education and Literacy recognises the Central Board of State Education (CBSE) and the National Institute of Open Schooling (NIOS) as public national boards, and the Indian Certificate of Secondary Education (ICSE) as a private national board.

Following the National Curriculum Framework for School Education (NCFSE) under the broader National Educational Policy (NEP), each board outlines its curriculum with general topics and state-specific focuses. While none of the aforementioned boards' guidelines include mandatory museum visits, field trips, or experiential learning, primary schools often include one

field trip a year to a local zoo or museum, but museum learning is not traditionally a significant part of the history classroom. Due to the lack of specific guidelines, the frequency of these visits varies greatly from school to school, but they are usually cursory in nature. While mandatory topics in history and civics across the three boards, such as the Indian freedom struggle, can be taught through frequent visits to relevant sites in each state or city even outside of the museum environment, the leftover "essentialist" (Rajvanshi, 2016) view of knowledge, a remnant of colonial systems, remains ingrained in traditional Indian educational systems. Focusing on rote learning, memory, mathematics, and structure (Sureshchandra, 1983), national boards don't usually include experiential learning as a regular part of education.

This, however, only applies to the traditional national boards; based on a study by the Indian Institute of Bombay, there have been several local experiments in alternative education in twenty-first century India. Stating that "From the Vedas onwards, ours has been an educational culture firmly dug into the bedrock of 'received' knowledge," (Bhattacharya, 2010) and going on to explain the damaging impacts the country's colonial history has had on prolonging this trend, Bhattacharya aims to highlight several alternatives by interviewing educational experts about the same. While Indian alternative education systems do exist, they tend to follow the open Gurukul approach in institutions such as the Sri Aurobindo International Centre of Education and Jiddu Krishnamurthy schools. Their emphasis on experiential learning is more nature-specific, rather than reliant on material culture.

India does, on the other hand, have several schools that have adapted international approaches to alternative education with an emphasis on Indian culture. With the examples of Navnirmiti's 'Do and Discover' approach to mathematics regardless of the board, Tridha's IGCSE-based Rudolf-Steiner approach to astronomy and geology, and Kendriya Vidyalaya Sangathan's unplugged approach to modern education providing the basis for comparison when their students take the same standardised exams after years of alternative learning, Bhattacharya hopes to make alternative education credible and push for the inclusion of experiential learning in all aspects of Indian education as it shifts away from complete emphasis on academics. Constantly stressing the importance of the children working with their hands and exploring tactile displays of the content they are being taught, Bhattacharya considers the importance of material culture and, by extension, museum learning in the contextualising, understanding, and subsequent retention of cultural knowledge at an early age.

While there are certainly limitations to the practical inclusion of museum visits in the case of rural schools that may find museums geographically inaccessible, the Indian Ministry of Culture, in collaboration with the Government of India's Ministry of Education have collaborated with national museums to find innovative solutions to the same including travel museums, teacher education programmes, and digital catalogues of museum collections. The next section will explore specific Indian public museums' outreach and accessibility initiatives designed to aid the active inclusion of museum learning in national education in greater detail.

Theme III - Museums in Modern India and their Educational Initiatives:

Since the introduction of the Museum Grant Scheme of 2021 by the Indian Ministry of Culture, which aims to: (a) Set up new Museums by Central and State Governments, historical societies, autonomous local cultural bodies, and private collection trusts registered under the Societies Act at the regional, state and district level, (b) Strengthen and modernise existing museums, (c) digitise art objects in museums across the country to made catalogues available virtually, and (d) build the capacity of museum professionals, public museums in India have undertaken more public outreach initiatives. This section of the paper will examine specific examples of Indian museums and their outreach initiatives, evaluating the same with a focus on their educational implications.

With reference to science museums, run by the Ministry of Culture under the National Council of Science Museums (NCSM), the Nehru Science Centre (NSC) in Mumbai is known for their STEM-related outreach initiatives and competitions. In addition to their 2023 Innovation Festival and Western India Science Fair, which had over 10000 attendees, their attempts to make scientific knowledge accessible extends to the digital space with monthly popular science lectures. Hosted offline and streamed by the auditorium of the centre, these lectures cover topics such as the role of artificial intelligence in Indian society (Dr. Anupam Goha, IIT-Bombay), the future of transportation (Dr. Anita Sengupta, USC), and nanotechnology (Dr. Kinshuk Dasgupta, BARC), and are completely free to audience members, usually resulting in an audience of between 200 and 1300. Recognising the need to collaborate with educational institutions in order to truly connect with younger audiences, the museum also offers experimental science demonstration sessions with schools upon request. Using the competitive nature of Indian education to increase the perceived educational value of such programmes, their Inter-school Science Quiz in collaboration with the Rotary Club of Bombay in both Marathi and English, as well as the International Astronomy Olympiad under the NCSM and the Ministry of Culture have increased their role in education directly, lending credibility to several future initiatives by actively integrating museums and education. Even though they have consistently focused on outreach initiatives with annual activity reports and several approaches to the same, the visitorship numbers reduced substantially due to the COVID-19 pandemic (Nehru Science Centre, 2022), but have been recovering steadily since as the museum uses technology to focus on publicity.

The National Museum of Natural History (NMNH) in New Delhi, on the other hand, divides their educational approaches to museums into four categories: interpretation, extension, in-reach, and outreach. With four regional offices, or Regional Museums of Natural History, in Mysore, Bhopal, Bhubaneswar, and Sawai Madhopur, the NMNH focuses on Teacher Orientation Programmes to make museum learning accessible at a local level. Their quarterly training sessions cover a range of environmental and conservation-related issues such as marsh edge erosion, desertification and sustainable forestry laws with reference to how they can be explained to children through the museum's outdoor exhibits. Run by the Ministry of Environments, Forests, and Climate change in collaboration with the Ministry of Education, the

museum's mission to communicate Indian's zoological, botanical, and environmental history has led to substantial success at the local level, but most of the main collection was destroyed in a fire in 2016, leading to a lack of sufficient statistical data for a quantitative comparison of visitorship and growth.

The Chhatrapati Shivaji Maharaj Vastu Sangrahalaya in Mumbai (CSMVS; originally named the Prince of Wales Museum), which received the 'Award of Excellence' at the United Nations Educational, Scientific and Cultural Organisation (UNESCO) Asia-Pacific Awards for Cultural Heritage Conservation in 2022, has a range of outreach programmes. The 'Museum on Wheels' project, for instance, has received international praise for its attempt to make museum artefacts accessible to the general public with the slogan "If you can't come to the museum, the museum will come to you." Equipped with two large air-conditioned city buses, the travelling collection of antiquities is curated with Maharashtrian state curricula in mind, focusing on the development of physical currency, Indian space exploration, and the remnants of princely states. Expanding their reach to the neighbouring states of Goa, Gujarat, Kolkata, and Telangana in collaboration with Teach for India, the National Centre for Performing Arts (NCPA), Nrityanjali, the Kendriya Vidyalaya group of institutions, the Bhabha Atomic Research Centre, the Indian Institute of Technology (IIT) Mumbai, and the Rotary Club of Bombay. Successfully having reached nearly 1,400,000 citizens in person with an additional 116,000 virtually, this initiative has increased museum visitorship substantially. Their children's museum and creative centre focuses almost exclusively on bridging the gap between museum-based learning and everyday education in India. Described as a "creative cultural lab," the space hosts a dynamic slate of month-long exhibitions, ranging from the evolution of ISRO, to Indian folk culture, to entomology. Their Sustained Enrichment Programme initiative offers educational institutions the chance to collaborate with the museum's education team by designed an eight session enrichment programme relevant to the curriculum of a particular group through interactive workshops that aim to combine the analysis of material culture with the use of technology to maintain relevance while simultaneously giving children complete creative control and responsibility of their learning.

All the museums mentioned acknowledge the presence of hundreds of regional languages, and while they cannot provide translations for each one, the museums all have signs in English and the state language (eg. Marathi for CSMVS and NSC) for each exhibit. This enables them to collaborate with a much larger group of schools where children are taught in different languages, increasing their prospective audience. Since they all offer some form of a teacher training programme, their flexible approach to learning allows them to adjust to the socio-economic circumstances of a school's students, taking their access to technology, geographical location, and curriculum into account to optimise museum-based learning.

Implications

Redefining the type of knowledge available in museums could certainly help increase their relevance to educational institutions. Museums' outreach initiatives, when successful, lead

to the development of cultural knowledge, enabling students to learn about their own culture when visiting an institution for what seem like solely academic purposes. With reference to the Salla Museum of War and Reconstruction study discussed in the first theme of this paper and the example of the Chhatrapati Shivaji Maharaj Vastu Sangrahalaya's recent 'Rhizome: Tracing Ecocultural Identities' project, museums can be spaces for essential conversations that may not translate as well in rigid, formal educational settings. Categorised as a form of accessible artistic research, the Rhizome initiative invited fourteen local artists to create site-specific installations that aimed to bridge the gap between art, culture, history, and education, "encourag[ing] ways to relook at the rhizomatic connections as well as the disparity and discord, rising due to the shifts in perception" (Thacker, 2023). Focusing on the themes of modern consumerism, the role of organised religion in Indian society, the casteist imbalance of ecological responsibility, and decolonisation through a collective reconnection with the natural world and its cycles, the three-month long project has drawn a vastly different crowd to the museum with a regrown passion for collective cultural learning, especially given the museum's central location next to the Jehangir Art Gallery in the Kala Ghoda art district of Mumbai. Similarly, the Salla Museum of War and Reconstruction urged two distinctly opposite groups, primary students and a local seniors' group, to learn from each other through an exploration of the evolution of cultural heritage, discussing the history of their identities and analysing how they were shaped from the Prehistoric Ages to the twenty-first century and its several technological revolutions.

While Indian cultural preservation and appreciation have never really been threatened with locations such as the National Centre of Performing Arts and the newly opened Nita Mukesh Ambani Cultural Centre in Mumbai, it is clear that neither resources nor availability are the problem with these sources of knowledge; it is a combination of inaccessibility, received irrelevance, and a lack of credibility in formal education that lead to lower visitorship. The combination of these spaces with the traditional museum helps increase their value to educational institutions regardless of their curricula with increased flexibility, allowing students to actively learn about modern problems in a credible setting. In the Indian context, where each state has a distinct cultural identity, the Finnish model of volunteer-run local museums could be implemented by making use of the pre-existing teacher education programmes offered at all of the museums discussed in this paper; this allows for the reduction of the issue of inaccessibility, the possibility to translate and tailor content to the exact syllabus and level of a class, and offer teachers complete control of the information they teach in a more interactive manner. With museums such as the Patang Kite Museum in Ahmedabad, the NIMHANS Brain Museum in Bengaluru, the interactive Museum of Indian History in Bengaluru, the Railway Museum in New Delhi, and the Black Magic and Witchcraft Museum in Mayong, for instance, India has an extensive variety of niche local museums to offer, and while that is highly beneficial in the preservation of cultural heritage, it cannot be generalised to the extent of standardisation needed for it to be entombed in the official national curricula.

That being said, one must consider the fact that international models are not always generalisable to the Indian context; programmes as simple to execute as the American high

school summer internships at museums, while present, are rare in India due to labour regulations, administrative struggles, and quite simply, a lower demand since museums have not been a part of education and are not viewed as directly valuable work experience as a result unless someone is particularly interested in pursuing history, archaeology, anthropology, art history or museology. According to Tejshvi Jain, an art history graduate working with the 'ReReeti: Revitalising Museums' foundation, the reason for low visitorship is not a lack of opportunity, but "a lack of knowledge about such places coupled with a sense of doubt or fear about whether they will be allowed to enter such places, lack of museums nearby, lack of funds to visit these spaces, lack of time or other priorities at home (sports, entertainment, family functions), and lastly, genuine lack of interest."

Conclusion

While the role of museums in modern education can be traced back to their etymological roots, a combination of geographical, socio-cultural, and economic factors influence their visitorship and their role in education. While psychological studies and educational surveys highlight the importance of experiential learning through interactive sessions in improving the role of cognitive development, there is still a higher rate of museum integration in alternative educational pedagogies than in traditional education systems. While most national schools include an annual field trip to a local museum and Indian museums are constantly attempting to increase their educational value through special exhibitions, expert-led educational events, nature trails, science olympiads, and teacher education programmes, there remains a division between the two institutions that will most likely take a decade of dedicated reform to connect. Field trips often serve as extensions to the material covered in class for students to better contextualise their knowledge and realise its true value while simultaneously gaining a deeper appreciation for their own culture and heritage, as demonstrated by the Finnish Salla Museum of War and Reconstruction and the Indian Chhatrapati Shivaji Maharaj Vastu Sangrahalaya's outreach initiatives and innovative solutions to low student visitorship. In a place as diverse as India, where each state has a distinct cultural identity and sufficient government funding for museums, the establishment of local museums could prove to be beneficial, but one must consider the fact that they cannot be generalised to the extent of standardisation needed for them to be entombed in the official national curricula. Given the increasing importance given to museums under the Government of India's Ministry of Culture in addition to each museum's individual initiatives, museums show great promise of inextricable inclusion in the future of Indian education.

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Predicting Close Prices of FAANG Companies with Multiple Linear Regression By Sharvari Vartak

Abstract

This paper explores a predictive model of the prices of FAANG stocks—Facebook, Apple, Amazon, Netflix, and Google using multiple linear regression. The date, consumer price index (CPI), Standard & Poor's 500 Index (S&P 500), National Association of Securities Dealers Automated Quotations (NASDAQ), and producer price index (PPI) were considered predictors of the closing stock price. The resulting coefficients were reasoned using economic trends. The model reveals how date and NASDAQ were large indicators of the closing value. Percent errors for the model's prediction were calculated to demonstrate the model's accuracy, along with improvements that can be implemented in future models. Furthermore, the paper highlights how the model is applicable to other scenarios as it was built off of common economic variables. These results can help provide insight on future company trends to investors.

Introduction

As companies and the economy grow, the relationship between many economic indicators and stock prices becomes increasingly complex. The FAANG stocks,which include Facebook (now Meta), Amazon, Apple, Netflix, and Google (now Alphabet) represent some of the most prominent companies in the technology and media sectors. Each company within the FAANG group possesses unique characteristics that contribute to its standing in the stock market. Facebook, a global social media giant, has revolutionized communication by connecting billions of people around the world. It went public in 2012 and currently has a market capitalization of 747.68 billion USD. Amazon, an e-commerce powerhouse, has transformed the online shopping experiences. This company became publicly traded in 1997 and has a market cap of 1.33 trillion USD. Apple has dominated the technology industry through hardware and software innovation. Apple went public in 1980 and has the highest market cap of 3.00 trillion USD. Netflix has transformed the entertainment industry by offering on-demand content consumption after going public in 2002 and with a current market cap of 195.55 billion USD. Lastly, Google exists as a notable search engine which has shaped the way people access information. This company went public in 2004 and has a market cap of 1.53 trillion USD.

This research explores the impact of economic variables on the stock prices of FAANG companies through multiple linear regressions to demonstrate the dynamics that influence the closing value of these stocks on the last trading day of the month. For the predictive model, several economic variables that impact stock market movements were chosen. These variables include Consumer Price Index (CPI), interest rates, stock indices such as NASDAQ, S&P 500, and the Producer Price Index (PPI). Each of these variables carries valuable information regarding the overall state of the economy, investor sentiment, and market conditions. By incorporating these variables into predictions, the interplay between the economic landscape and these companies' stock performance can be captured.

By analyzing the coefficients and intercept derived from the regression model, we gain insights into the relative importance and direction of influence of each economic variable. Furthermore, the model provides a framework for predicting future stock prices, allowing investors to make informed decisions based on anticipated trends. This information empowers market participants to adjust their investment strategies and gain a deeper understanding of the factors driving stock price movements.

Methodology

A multiple linear regression model was used to capture the potential linear relationships between the independent variables (i.e., Date, CPI) and the dependent variable (stock price). This approach allows us to explore the combined impact of multiple variables on stock price movements.

The equation for this linear regression is as follows:

$$\text{Close Price} = \text{Date} * x_{date} + \text{CPI} * x_{CPI} + \text{S\&P 500} * x_{S\&P500} + \text{NASDAQ} * x_{NASDAQ} + \text{PPI} * x_{PPI}$$

CPI measures changes in the average prices for goods and services over time. It serves as a proxy for inflation and helps to gauge the purchasing power of consumers. Additionally, stock indices such as NASDAQ and S&P 500 serve as indicators of market performance. Movements in these indices can influence individual stock prices, including these companies. The Producer Price Index (PPI) tracks changes in prices encountered by producers. It offers insights into input costs, production levels, and overall industry performance, which can affect stock values. By considering these economic variables, a relationship between such indicators and stock prices can be found. .

The ‘Close’ values of FAANG stocks serve as markers to evaluate market performance. By investigating the relationship between economic variables and the close values of the FAANG stocks, this research aims to provide valuable insights for investors, analysts, and market participants. By using monthly data, the model can more accurately predict long term trends.

In order to test the model’s accuracy, the values of economic variables for the desired range were used to predict its corresponding close stock price. The values for such variables were multiplied by their corresponding coefficients that the multiple linear regression model output.

For FAANG companies, the model was trained on monthly data from January of 2005 to December of 2020. Facebook was trained from May 2012, the year it went public. The model was used to predict monthly prices for 2021 and 2022. Splits and dividends were accounted for by scaling the prices before and after such changes. All economic variables were scaled between 0 and 1, so that each factor was weighed equally.

Variable	Least (0)	Greatest (1)
Date	2005	2020.92
CPI	190.7	260.47
S&P 500	29.33	70.06
NASDAQ	14	136.3
PPI	156	204.9

The data for this model was taken from Kaggle databases.

Results

The multiple linear regression yielded the following coefficients to model FAANG companies' close prices.

	Date	CPI	S&P500	NASDAQ	PPI	Intercept
Facebook	1.58	-0.233	-0.0951	0.140	0.112	-0.652
Apple	0.245	-0.00665	-0.0932	0.661	0.0485	-0.0311
Amazon	0.680	-0.279	-0.139	0.668	-0.0711	-0.00877
Netflix	1.03	-0.516	-0.127	0.705	-0.108	-0.0173
Google	1.00	-0.603	-0.0241	0.594	-0.0109	0.0185

*rounded at 3 significant figures

The percent errors for 2021 and 2022 based on the models prediction on FAANG companies are listed below.

Percent Error of Predicted Close vs Actual Close

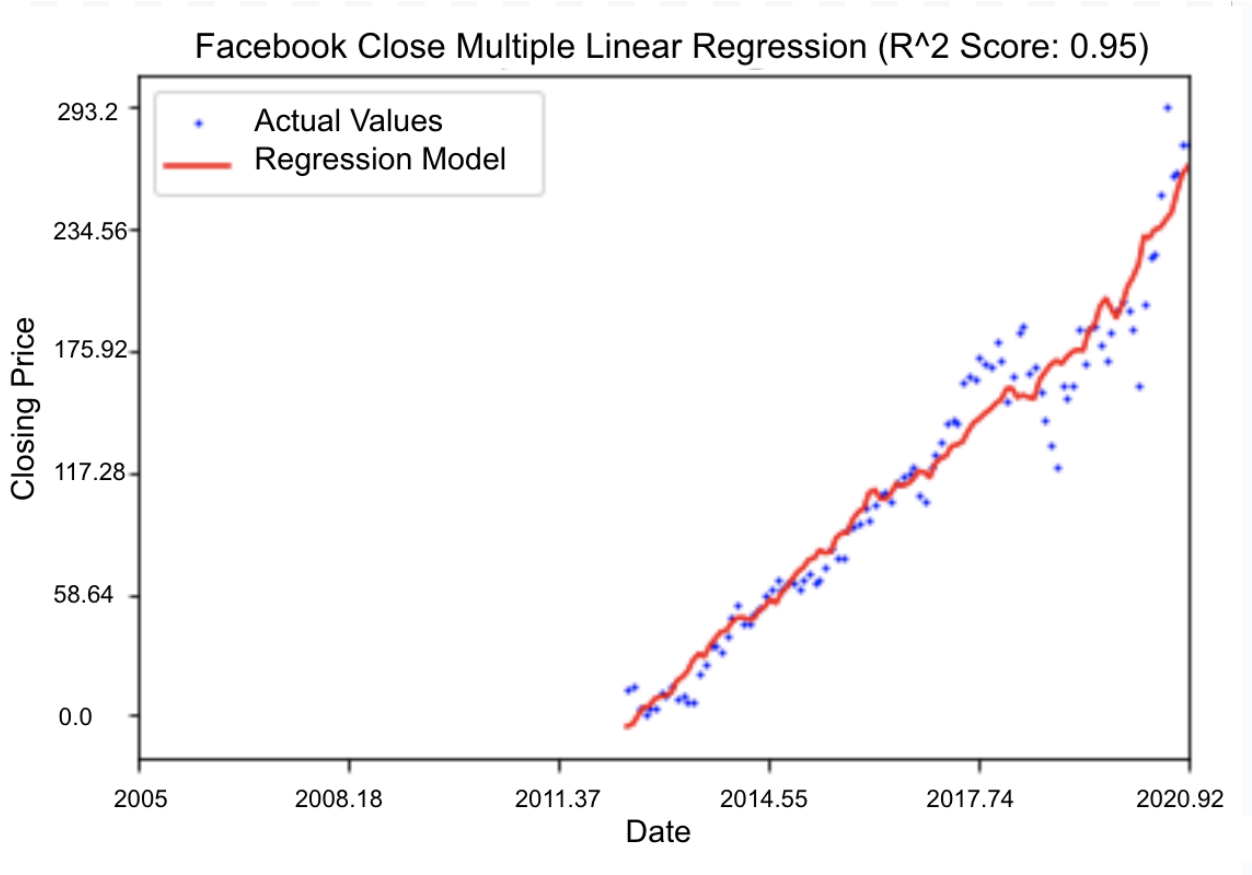
	Facebook	Apple	Amazon	Netflix	Google
Jan 2021	28.18%	11.97%	-3.09%	33.75%	-22.56%
Feb 2021	30.48%	8.57%	-5.98%	24.74%	-24.43%
Mar 2021	41.22%	1.64%	1.59%	28.15%	-36.96%

Apr 2021	28.95%	2.78%	-4.07%	23.54%	-29.37%
May 2021	22.56%	-5.56%	5.80%	25.09%	-25.98%
Jun 2021	22.62%	2.65%	0.33%	18.84%	-25.81%
Jul 2021	14.20%	7.82%	4.73%	13.61%	-22.56%
Aug 2021	1.29%	10.58%	1.99%	7.93%	-16.45%
Sept 2021	11.88%	2.88%	7.17%	13.31%	-25.74%
Oct 2021	11.71%	6.25%	6.74%	19.53%	-20.70%
Nov 2021	6.70%	18.89%	1.34%	15.90%	-13.66%
Dec 2021	7.80%	29.94%	4.35%	5.88%	-13.61%
Jan 2021	13.90%	24.20%	15.72%	8.38%	-10.40%
Feb 2021	13.54%	19.35%	11.52%	5.64%	-0.28%
Mar 2021	1.54%	26.60%	5.81%	8.62%	0.87%
Apr 2021	-6.31%	10.26%	31.31%	13.77%	14.28%
May 2021	-6.38%	3.23%	33.18%	16.59%	13.32%
Jun 2021	-11.33%	-4.52%	40.05%	12.22%	18.55%
Jul 2021	-14.07%	12.04%	26.84%	15.09%	25.09%
Aug 2021	-20.89%	6.46%	32.05%	8.39%	31.55%
Sept 2021	-6.65%	-7.47%	40.75%	3.33%	19.34%
Oct 2021	-1.50%	3.09%	52.07%	-9.58%	32.39%
Nov 2021	-4.57%	2.87%	47.90%	-5.92%	27.69%
Dec 2021	-7.35%	-11.04%	54.30%	2.35%	27.62%

Positive errors indicate predicted values were higher than actual values, while negative errors indicate predicted values were less than actual closing values. For Meta, the model overestimates the closing value in the beginning of the prediction time window, but this gradually decreases to be around or slightly underestimating. For Facebook, the percent error

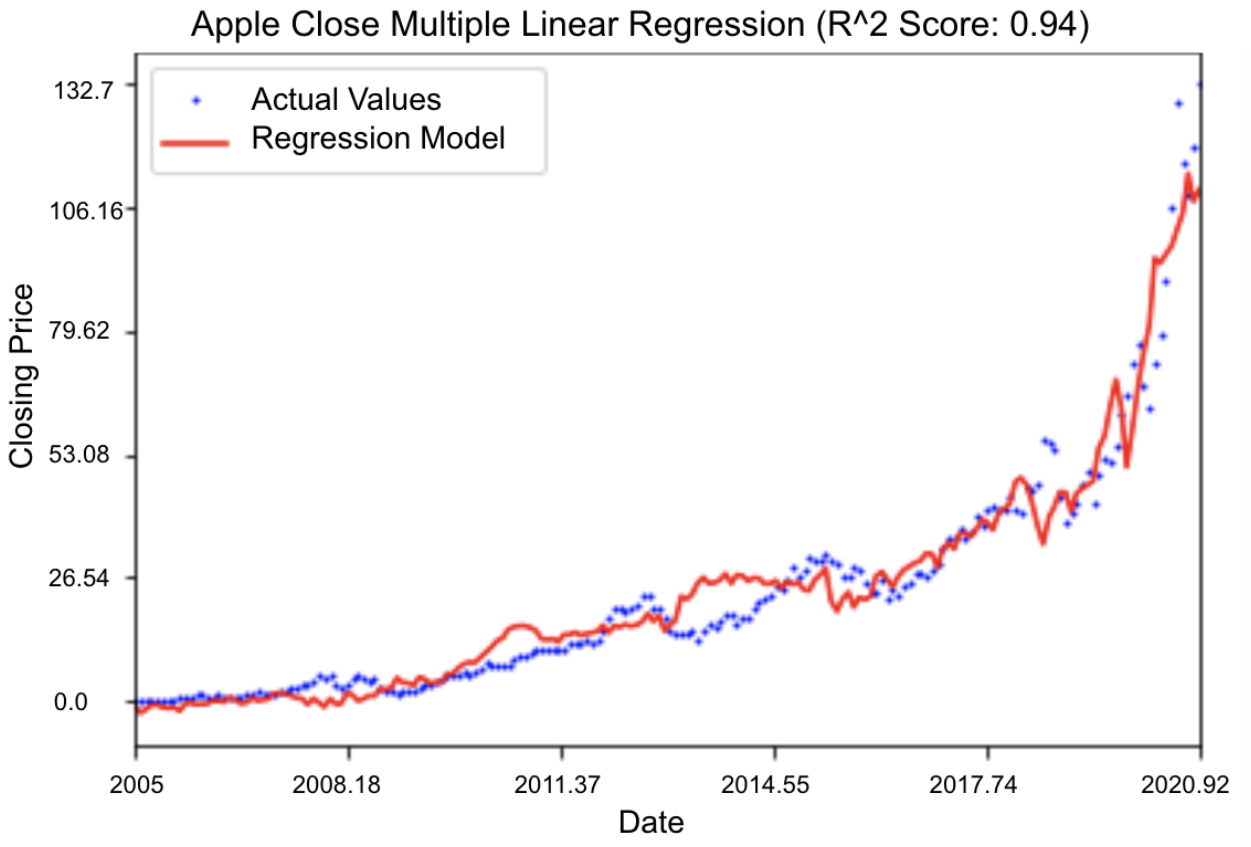
with the smallest magnitude is 1.29% and the greatest is 28.18%. For Apple, there is no clear pattern within the percent errors with the lowest magnitude being 1.64% and the highest being 26.6%. For Amazon, the model consistently overestimates the closing prices with the smallest magnitude being 0.33% and the largest being 54.30. The percent errors grow overtime, suggesting compounding errors and a dip in growth by Amazon. For Netflix, the model appears to consistently overestimate the closing price with the smallest percent error being 2.35% and the largest being 33.75%. For Google, the model appears to consistently underestimate the closing value with the lowest magnitude being 0.28% and the largest being 36.96%.

Facebook



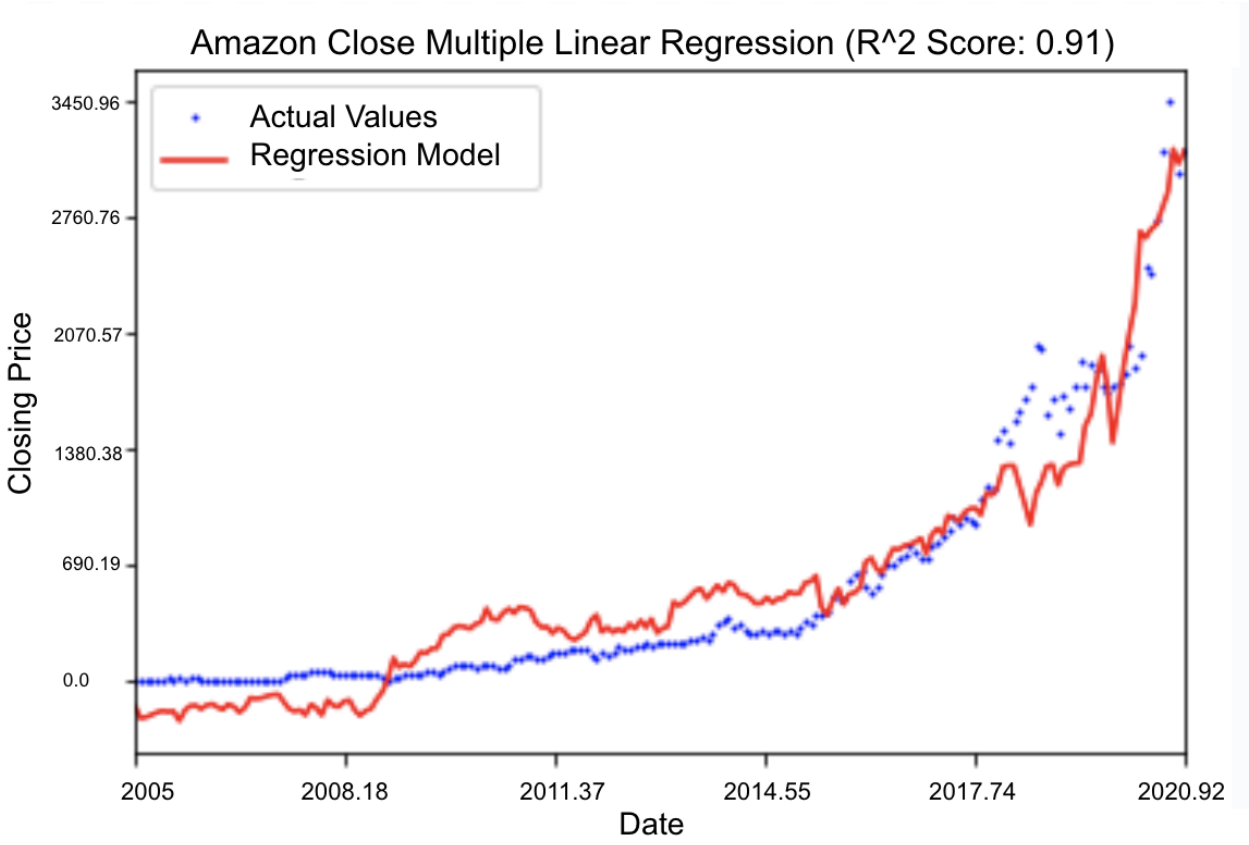
Multiple linear regression model for close price of Facebook from May 2012 to December 2020. Dates are represented through decimals (eg. 2020.92 corresponds to December 2020). In this regression, 95% of the variation in close price can be explained with our explanatory variables.

Apple



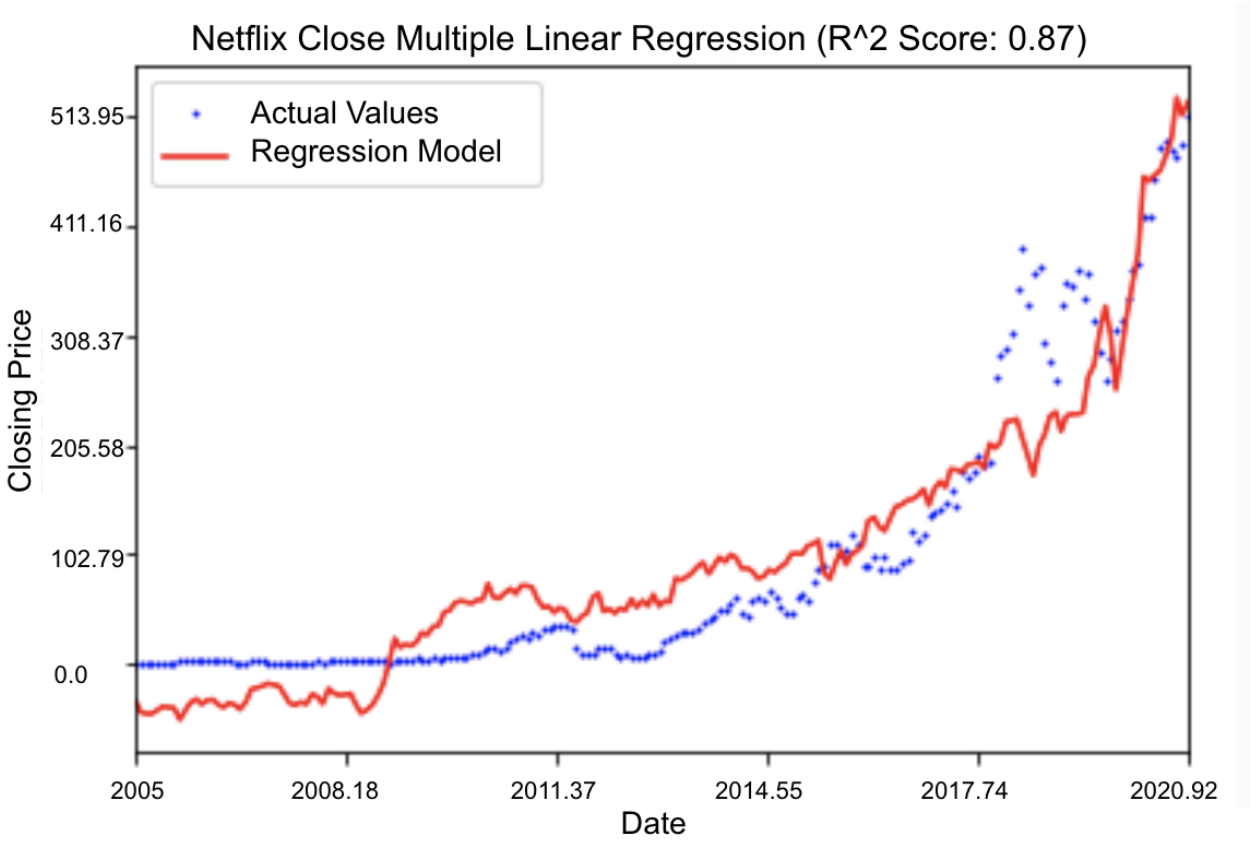
Multiple linear regression model for close price of Apple from January 2005 to December 2020. Dates are represented through decimals (eg. 2020.92 corresponds to December 2020). In this regression, 94% of the variation in close price can be explained with our explanatory variables.

Amazon



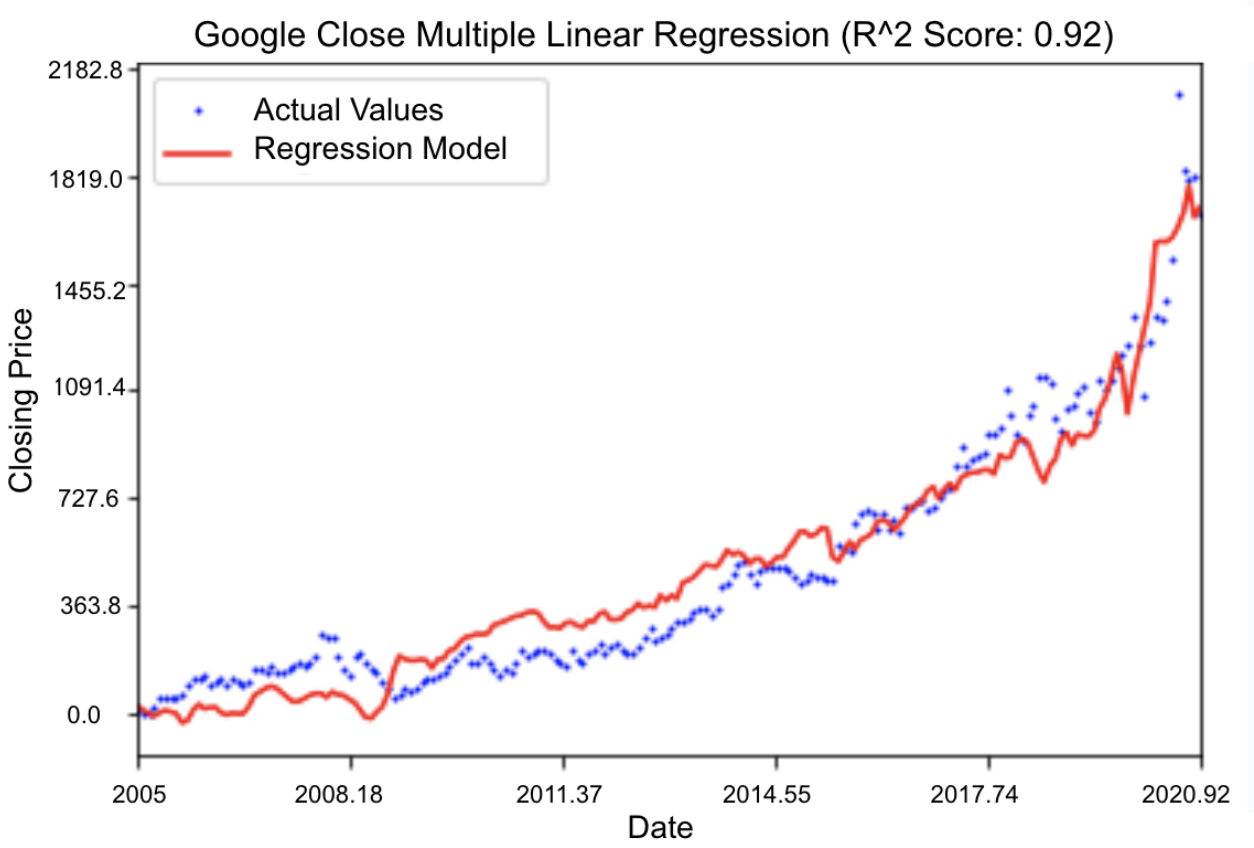
Multiple linear regression model for close price of Amazon from January 2005 to December 2020. Dates are represented through decimals (eg. 2020.92 corresponds to December 2020). In this regression, 91% of the variation in close price can be explained with our explanatory variables.

Netfli



Multiple linear regression model for close price of Amazon from January 2005 to December 2020. Dates are represented through decimals (eg. 2020.92 corresponds to December 2020). In this regression, 87% of the variation in close price can be explained with our explanatory variables.

Google



Multiple linear regression model for close price of Google from January 2005 to December 2020. Dates are represented through decimals (eg. 2020.92 corresponds to December 2020). In this regression, 92% of the variation in close price can be explained with our explanatory variables.

Discussion

When analyzing the coefficients for the economic variables in the multiple linear regression models for predicting Facebook, Apple, Amazon, Netflix, and Google stocks, several general trends emerge:

Firstly, the coefficient for the Date variable is positive for all five companies, indicating that stock prices tend to increase over time as the companies expand. This suggests a general upward trend in the stock prices of these companies and expansion of these tech-centered businesses.

Secondly, the coefficients for CPI consistently show a negative relationship with the predicted stock prices across the companies. This implies that as the CPI increases, indicating higher inflation, the predicted stock price tends to decrease. Inflation can potentially affect consumer spending and overall economic conditions, which may impact stock prices negatively.

Additionally, the coefficients for the S&P 500 index exhibit negative relationships with the predicted stock prices. This stock index is an indicator of the overall economic conditions.

However, the small magnitudes of these coefficients indicate the possibility of confounding with other economic variables, particularly the NASDAQ index, which follow a similar pattern.

The coefficients for the NASDAQ index consistently show large positive relationships with the predicted stock prices across all companies. Because these companies and NASDAQ are both technology-oriented, general growth in this industry will be reflected in both indices. This reflects the influence of broader industry trends and investor sentiment in the technology sector.

Regarding the PPI variable, the coefficients show mixed results. While some coefficients suggest a negative relationship with the predicted stock prices, others indicate positive or negligible effects. This suggests that the impact of PPI on stock prices may be more nuanced and dependent on other factors specific to each company. There may also be confounding between PPI and CPI as the two trend similarly.

Throughout all five companies, the date and NASDAQ variables had the largest coefficients. The date suggests that all of these companies are growing over time, while NASDAQ represents the technology industry's overall performance, making it a large contributor to this regression. The one exception to this was Netflix, which also had a high magnitude CPI coefficient, indicating that inflation creates a notable effect on its stock price.

In summary, the analysis of the coefficients reveals that the Date variable consistently exhibits a positive relationship with stock prices across all companies. The CPI variable generally shows a negative relationship, reflecting the impact of inflation. The S&P 500 coefficients indicate a potential negative relationship, albeit with small magnitudes. The NASDAQ index consistently demonstrates a positive impact on stock prices, indicating the influence of technology industry trends. The impact of the PPI variable appears to be more varied and less pronounced.

This linear regression model has several strengths. Firstly, the model allows for the simultaneous analysis of multiple variables, providing a comprehensive understanding of the factors that may influence Apple stock prices. By incorporating relevant economic indicators such as GDP, CPI, S&P500, NASDAQ, and PPI, the study ensures its real-world applicability, as these variables are influential in economic analyses. Moreover, the interpretability of the coefficients obtained from the regression model is valuable as it can help people choose when and how much to invest depending on the current economic factors.

This study faces certain limitations. Omitted variables present potential biases and impact the model's predictive power. Additionally, data limitations, such as the monthly frequency each variable was measured could affect the model's accuracy and generalizability. Violations of model assumptions, such as normality and linearity, should also be considered, as these can affect the validity of the regression results. To further refine the model, various other economic variables could also be used. For example, incorporating release dates for companies' products could provide valuable insight on when certain fluctuations are to occur. Additionally, world events, such as the pandemic, that could affect the economy at large should be considered.

Conclusion

This research project aimed to predict FAANG (Facebook, Apple, Amazon, Netflix, Google) stocks using multiple linear regression. The study explored the impact of economic variables on stock prices and their potential applicability to other domains. The results revealed that the NASDAQ index had a large positive correlation with the predicted stock prices of FAANG companies. On the other hand, variables like CPI and S&P 500 showed negative coefficients, indicating an inverse relationship. We also see possible confounding between similar variables like CPI and PPI. The findings align with economic reasoning and provide insights into the dynamics of stock market prediction.

This model developed for FAANG stocks can be applied to other similar financial tasks. Because many stocks exhibit patterns similar to these five, common economic variables were used, and the companies all exist as a part of the technology-industry, this predictive model can be expanded towards other companies in the same industry. By using these predictions, investors can choose when an optimal time to invest in a certain technology-focused company is.

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CTE in Professional Football: Epidemiology, Prevention, and Player Safety By Christophe Chau

Abstract

This research paper aims to provide a comprehensive review of the relationship between football and the development of Chronic Traumatic Encephalopathy (CTE) resulting from repeated traumatic brain injuries (TBIs), including investigating the significance of CTE as a neurodegenerative disease, examining past and present research into its epidemiology and prevention, and emphasizing the need for ongoing studies and urgency in prioritizing player safety. It calls upon coaches, players, and organizations like the NFL to work collectively towards reducing the incidence and impact of CTE. By fostering a safer environment, promoting a collaborative effort, and advancing our understanding of the relationship between football and CTE, a safer future for all athletes may be possible.

Introduction

In 2017, researchers at Boston University examined the prevalence of chronic traumatic encephalopathy (CTE) in 202 former football players across professional, semi-professional, collegiate, and high school levels of play. They found evidence of CTE in 87% of all brains examined, including 91% in NFL players, 88% in CFL (Canadian Football League) players, 64% in semi-professional players, 91% in collegiate football players, and 21% in high-school players [4]. In recent years, high-profile cases of former NFL players affected by CTE have prompted further study of the neurological condition while also further raising concerns about player safety in football and other contact sports. As a result, many teams and individuals have called for changes in the way football is played and managed, with a focus on reducing unnecessary contact. Meanwhile, ongoing research continues to explore the long-term effects of repetitive head trauma and the best ways to both diagnose and treat CTE. With the prevalence of football being played at the professional, collegiate, and youth levels, at an estimated 5.23 million players per year, a review of its relationship to the development of CTE is necessary [17].

Methods

When researching the relationship between American football and the development of CTE, evidence points to a link between repetitive head trauma and the onset of neurodegenerative symptoms [1]. To reduce the likelihood of this condition for at-risk athletes, it is crucial to implement preventative measures including improved safety equipment and increased education about the dangers of contact sports. To date, there is a continued need to review the current status of such preventative efforts, while also taking into account the existing cultural narrative surrounding football and CTE. This review aims to discuss the aforementioned high-profile cases involving NFL players, the current state of CTE preventative efforts, and how these findings together can be used to improve football player safety.

To conduct this review, a search was conducted on PubMed, major news outlet sites, and official institutes of higher education from January to April 2023, using the search terms "NFL," "CTE," and "player safety." Only papers of the document type newspaper or journal article published between 2012 and 2022 were included. The review excluded articles that discussed other forms of traumatic brain injuries and cases of CTE outside of football, such as those of CTE occurring in hockey players. Finally, 17 articles, including 8 from the initial search and 9 additional articles found by cross-referencing, were analyzed for research methodology, study credibility, the scope of investigation, and risk factors evaluated.

What is CTE?

Chronic Traumatic Encephalopathy, known as CTE, is a neurodegenerative disease that results from repeated traumatic brain injuries (TBIs). TBIs are caused by outside forces including blows or jolts to the brain, and they can result in short-term issues in brain function and processing. With enough instances of TBIs, CTE can arise, causing neuron loss and the accumulation of protein/plaque deposits within the brain [18]. Symptoms of CTE can often take years or decades to develop and can worsen over time. These symptoms can be categorized into four major fields: cognitive, behavioral, neurologic, and mood. Cognitive symptoms can range from short-term memory deficits to dementia, while behavioral symptoms can include substance abuse, suicidal thoughts, and violent tendencies. Neurologic symptoms consist of Parkinson-like afflictions (uncontrollable movements), dysarthric speech, and mood changes, including depression, irritability, or suicidal thoughts [16]. Individuals typically associated with being at risk for CTE include athletes in contact sports, and most notably, American football players, due to the violent nature of the sport and the frequency of head impact [10].

CTE is a progressive disease, typically unfolding over several stages with worsening symptoms. In stage 1 of CTE, the buildup of tau protein remains isolated in the frontal lobe of the brain (responsible for executive function and cognition), and victims of stage 1 CTE can often experience headaches, difficulty concentrating, or possibly even no symptoms at all. In stage 2, symptoms worsen as the tau protein begins impacting more nerve cells, leading to mood swings and depression. In stage 3, greater amounts of tau protein build up and expand to the temporal lobe of the brain, impairing emotion and memory. Common symptoms of stage 3 CTE include confusion, memory loss, and general cognitive impairment. Stage 4 is the final and most severe stage, where the buildup of tau protein overwhelms the brain, causing shrinkage and further damaging nerve cells, leading to severe memory loss and dementia [13]. Of note, CTE can only be diagnosed and staged post-mortem from brain samples, limiting its surveillance to clinical manifestations (reference post-mortem).

History

The history of this condition can be dated back to Dr. Harrison Martland, who in 1928, coined the term: “punch drunk syndrome” Punch drunk syndrome symptoms included slurred

speech and faltering gait and were often diagnosed in professional boxers who fought with aggressiveness over skill or those who were frequently knocked out in training. In the years following Martland's initial findings, J.A. Millspaugh and C.B. Courville would expand on his research and reclassify punch drunk syndrome as dementia pugilistica. Later on, Courville referred to it as the psychopathic deterioration of pugilists, or those inclined to fight. In 1949, the British neurologist Macdonald Critchley built upon their investigations in his study presented in the Lancet. While examining a case study of a retired boxer exhibiting symptoms of neurological decay, Critchley used the term Chronic Traumatic Encephalopathy for the first time [6]. In more recent decades, the research of Dr. Bennet Omalu has proved critical. While his groundbreaking discovery of CTE in former Pittsburgh Steeler Mike Webster sparked significant controversy, it also led to further research and progress in understanding the condition [9]. Understanding the history of CTE and its evolution in sports sheds light on the gravity of the condition and the need for further research into its diagnosis and treatment.

Developments

The Diagnose CTE Research Project at Boston University has provided new insight into possible early pre-mortem CTE detection methods. Using positron emission tomography (PET) scans, researchers have been able to detect the buildup of tau proteins, an early marker of CTE. The PET scans use radioactive tracers to produce gamma rays which are then detected by the scanner. Researchers hope that these tracers bind to proteins present in patients with CTE, which would allow them to monitor the condition within the brain. Although the process is years away from providing definitive diagnoses, it serves as a benchmark for future advances in early detection [2]. Additionally, scientists from the University of Southern Australia have developed a new drug that they hope could mitigate, and even prevent the symptoms of CTE. When the brain experiences a head injury, it releases substance P, a neurotransmitter; this process causes the buildup of tau protein, prevalent in cases of CTE. However, scientists believe that if substance P were to be inhibited by a drug, the symptoms of CTE could be prevented. Currently, the drug has passed animal testing but is still awaiting human clinical trials [12].

Prevention

Recent advances in medicine have given way to further developments in education and prevention efforts. While there is no definitive way to prevent CTE, it is possible to minimize the severity and volume of head injuries that could lead to CTE. This can be achieved through dedicated education of coaches and athletes, proper “return to play” protocols from injury, and protective equipment. With regard to the latter element, new studies have provided insight into the protective potential of certain helmets. A study in the Journal of Neurosurgery compiled data recorded from 8 college football teams to determine whether different helmet designs affected the incidence of concussions. The study compared the Riddell VSR4 against the Riddell Revolution helmet and concluded that the Revolution model provided more effective protection against concussions [15]. Despite this proof of concept, helmets today still have room for

improvement. At the University of Cincinnati, engineers have tested several helmet models and their ability to mitigate impacts. Although the majority of models tested similarly, they shared a glaring weakness at the back of the helmet, where players were most vulnerable. The researchers suggested that the shell and padding of the helmets could be adjusted in order to provide better protection for the wearer. However, they also conceded that more research both on and off the field was needed in order to fully determine the scope of the issue [11]. While developments in the helmet industry show promise, equipment is only one part of a multifaceted approach to preventing traumatic brain injuries.

Thus, prevention efforts must also be implemented, including education and proper management of head injuries. Athletes should be counseled on the risk factors that can contribute to the development of CTE, including history and severity of concussions, illicit substance use, alcoholism, pre-existing medical conditions, and genetic predisposition. Additionally, athletes should be encouraged to be transparent with their team about seeking treatment and reporting possible symptoms of a head injury/TBI. Likewise, coaches should receive training on identifying symptoms of TBI and CTE, and also be informed that the full scope of the latter condition has not yet been realized with premortem diagnosis technology still in its infancy. For players that have suffered previous head injuries, properly managing their ailments is vital to preventing further complications. In this area, coaches must be prepared to gradually re-introduce their athletes through the implementation of proper return-to-play protocols.

According to Mass General Brigham's rehabilitation protocol, the returning player must undergo several phases in order to be medically cleared to return. Phase one is initiated immediately after the injury and consists of rest and precautionary action in the case of any symptoms. Phase two suggests light activity to recondition the athlete and no contact in sports. Phase three is a continuation of the prescribed activity, still with no contact. Phase four transitions the athlete back into sports-specific activity with the ability to participate in drills, continuing with the theme of no contact. Finally, phase five is a full return to play and additional intervention, if necessary. This process is not linear and may require further patience as coaches monitor any signs or symptoms of concussion [14]. By taking preventative measures against head injuries, such as using the appropriate protective gear and implementing proper return-to-play protocols, the incidence of concussions and associated risks may be reduced. However, education remains a critical component in the fight against CTE. In addition to informing athletes and coaches about the risks of CTE, it is essential to teach them how to recognize and respond to symptoms of TBI.

Notable Cases

Despite improvements in medicine, the devastating effects of CTE continue to be observed, which has been highlighted by several recent cases in notable NFL players. The most infamous of which involves former Florida Gators and New England Patriots tight end, Aaron Hernandez. Hernandez was a star player at the University of Florida, helping lead the Gators to a national championship in 2008. In his final college season, he was a consensus All-American and

awarded the John Mackey Award for being the premier tight end in college football. In 2010, Hernandez was drafted by the New England Patriots and immediately made an impact on the field with a standout rookie season. Two years later, he would be instrumental in the Patriots' playoff run and subsequent Super Bowl appearance. Unfortunately, his career was cut short in part due to the damage he suffered on the field, and his decisions off the field. Hernandez, aged 27, died April 19th, 2017 by suicide. Prior to his death, Hernandez had reportedly deteriorated physically and mentally. On June 26, 2013, Hernandez was taken into police custody for the alleged murder of Odin Lloyd, a semi-professional football player who was dating the sister of his fiancée. During trial, new evidence emerged that linked Hernandez to a previous double homicide in 2012, leading to his conviction of first-degree murder among other charges. Throughout his trials, Hernandez reportedly exhibited symptoms of TBI/CTE such as depression, mood swings, and outbursts of violence. Hernandez would later plead not guilty but was sentenced to life in prison without parole. Upon autopsy examination, his brain showed signs of advanced stage 3 CTE with large amounts of tau protein buildup in addition to dilated ventricles, an atrophied fornix, and a shrunken brain [8].

Hernandez's case was instrumental in raising public awareness of the dangers of head trauma in football and bringing attention to the lack of concern over player safety by the NFL. However, this wasn't the first and, unfortunately, it wasn't the last instance of a former NFL player being diagnosed with CTE. In 2022, it was revealed that former Denver Broncos wide receiver Demaryius Thomas had also suffered from the disease. Thomas was drafted by the Denver Broncos in the 1st round of the 2010 NFL draft, and was an elite wide receiver in the NFL, making 4 Pro Bowls. Thomas played a pivotal role in the Broncos' 2013 season, which would see the team make the Super Bowl; in the championship game, Thomas would surpass a then Super Bowl record for most receptions with 13 along with 118 receiving yards and a touchdown. When the Broncos broke through and won Super Bowl 50, Demaryius Thomas continued to make an impact. On June 28, 2021, Thomas would announce his retirement, bringing his 10-year professional career to a close. However, in December of that year, Thomas, aged 33, would unexpectedly die from complications caused by a seizure [3]. After an autopsy, researchers at Boston University found lesions in his frontal and temporal lobes, diagnosing his brain with stage 2 CTE. Although his death was caused in part by prior off-field injuries, including a car crash and fall, those close to Thomas noted that his behavior and tendencies were symptomatic of CTE. Thomas had tried to seek help for his dementia, panic attacks, and mood swings, but was unable to be treated [7]. Demaryius Thomas's tragic death has since prompted the NFL to renew its commitment to player safety and develop new protocols to address the prevalence of head injuries. The league has pledged to invest hundreds of millions of dollars into helmet and concussion research [5]. While it is a step in the right direction, many argue that the NFL needs to do more to protect its players and prevent cases like those of Aaron Hernandez and Demaryius Thomas from happening in the future.

Discussion

The incidence of CTE in NFL players points to a link between repetitive head trauma and the onset of neurodegenerative symptoms. Although the primary risk factor for CTE is exposure to repeated TBI, it is not a perfect causation-to-correlation relationship. To reduce the likelihood of CTE, the implementation of preventative measures such as increased education and improved safety equipment is critical. The high-profile cases of NFL players diagnosed with CTE have raised awareness of the severity of the condition. Despite the current efforts being made to prevent CTE in football players, there is still much work to be done; there must be a concerted effort to educate coaches, players, and parents about the risks associated with contact sports. Additionally, there should be continued efforts to develop improved safety equipment that can better protect players from head trauma and minimize the risk of CTE. These efforts must be supported by the NFL to ensure that the cases of Aaron Hernandez, Demaryius Thomas, and others are not repeated.

Conclusion

The prevalence of CTE in football players, specifically at the professional level, is an ongoing issue that requires further research into its epidemiology and prevention. Although much progress has been made in recent years, player safety remains a priority. It is essential for all involved in the sport, including coaches, players, and organizations like the NFL, to work towards reducing the incidence and impact of CTE. By continuing to study the relationship between football and CTE, a safer future for all athletes may be possible.

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Rare Pediatric Neurology: We Need an Investigation By Annika Arya

Our brains are a vital organ, they make us, us. They allow our fates to be decided, our laughter to fill a room, our ideas to be shared and our love to be spread. Many individuals make decisions early in their lives that affect their brain health well into adulthood. Drinking, smoking, the use of recreational drugs, lack of physical movement, not properly fueling our bodies, inhaling toxins, traumatic head injuries, being surrounded with loud sounds and even loneliness can trigger a loss of brain cells. When we're young, often, we don't consider that these factors can colossally affect our futures. These bad habits can cause strokes, Alzheimer's, Dementia, different types of brain hemorrhage, Parkinson's disease, Multiple Sclerosis, Lateral Sclerosis, and other brain conditions that can be easier to prevent early on. Although some of these cases tend to be occasionally genetic, such as Lateral Sclerosis, Dementia and Aneurysmal Subarachnoid Hemorrhage, we are still able to access more research for treatments and early preventions, considering these diseases were discovered as early as the 1800s. We have over 100 years of research on all of these different brain conditions, but unfortunately, the same cannot be said for newer and more rare conditions.

Recently, two people in my life have suffered from brain incidents and conditions. One of my closest family friends, who I have known since birth, was recently diagnosed with an umbrella term of early-onset Dementia. Her Father is currently suffering from Dementia, and she suspects that her Father's condition may play a role in her diagnosis, or the fact that she drinks alcohol often. In her 50s, she is being warned of the damage to her brain, just before her third marriage and a new chapter in her life. Only 5 percent (2,500,000) of cases of Dementia get diagnosed before the age of 65. In 2021, it was reported that less than 0.64 percent (50,000,000) of the world's population suffers from dementia and 0.03 percent of the population is diagnosed with early onset dementia. Even with these small percentages, these numbers are large enough that when plugged into PubMed, the database for biomedical research, we receive around 8,133 results.

Another case of a loved one suffering from a brain incident or condition, was when one of my teenage friends was awoken during their sleep, unconscious and foaming at the mouth from an unknown and undiagnosable incident. They woke up with a Paramedic, an EMT, aiders and several police officers surrounding them. It took them hours to be discharged from the hospital, the doctors presumed this incident to be a seizure, but they did not have any solid evidence. Even after seeing a radiologist and cardiologist, no diagnosis was achieved. The CAT Scan reported that there was no hemorrhaging inside of their brain. Even with their father having sleep apnea, a disorder that causes breathing to halt during sleep, usually obstructive, produced by a collapsed or blocked airway, often causing unconsciousness and especially occurring in older and more overweight males. My friend is neither older nor overweight, so the doctors ruled this condition out. To this day, we still have no idea what this alarming experience was or what it was even caused by. Doctors, unsure, still *presume* it to be a seizure, having no solid evidence for this diagnosis.

Neuroscience research is often focused on neurological disorders that occur in older individuals, neglecting the overlooked and disregarded brain conditions that arise in younger individuals and frequently have unknown causes. The neurological disease, Rasmussen's Encephalitis (RE) is often a victim of being overlooked by Neuroscientists when conducting their research. Rasmussen's Encephalitis is a chronic and inflammatory disorder often affecting those under the age of 10. It typically affects one half of the brain, leads to cognitive decline, seizures and deficits. The initial stage is characterized by Focal seizures, these typically involve muscle activity affecting motor skills and occur from a specific part of the brain once nerve cells set out uncontrolled electrical signals. The second stage is Epilepsia Partialis Continua where the child experiences extended and repeated focal seizures. The third stage is neurological deficits appearing, paralysis, weakness in muscles, change in cognitive function, language distortion, changes in behavior and impaired motor skills occur in victims of Rasmussen's Encephalitis. The final stage is Hemiplegia, where victims can experience paralysis or weakness on one side of the body, this can affect coordination and impairment for a lifetime. The only treatment that has been discovered for Rasmussen's Encephalitis is a surgery that removes one part of the brain, which is a cerebral hemispherectomy that can lead to developmental problems, loss of vision, brain infection and bleeding, it can also lead a patient with permanent cognitive and motor impairment. Not only that, the surgery only has a 15% success rate of completely eliminating seizures.

Of the ⅛ of the the population that the UN states suffers from a neurological disorder (1.262 billion), only 31.25% of that number are children (394.375 million). It is understandable why a disease like Rasmussen's Encephalitis would have only 768 search results on PubMed (as of June 21st, 2023), considering that there are less than 500 cases worldwide. However, this case number does not account for the number of children that go undiagnosed with this disease and other undiscovered neurological disorders that occur in minors. So many chronic brain conditions are neglected due to the lack of research of the conditions that affect children and adolescents. A top American hospital, Cedars-Sinai, was unable to detect the cause of Rasmussen's Encephalitis and many write it off as an autoimmune response. There is no cure for this disease, even though it was discovered back in 1958. Of course, this discovery is not as early as when Hippocrates first encountered epilepsy, but the solid neurological research wasn’t done until John Hughlings Jackson laid the foundation for epilepsy research in 1890, noting seizures as “convulsions throughout one’s body”. As neurological research gets more advanced, the basis of Rasmussen's Encephalitis has yet to be discovered, let alone have a solid cure.

Of course, medicine is still improving and we are only so far into science research to be able to unravel the mysteries of our neurological systems. There is a smaller patient pool of children whose parents can notice these differences in our neurosystems early on. Children’s young brains are still developing so it can be more difficult to understand the contrast between healthy neurological conditions and toxic ones. There is a lack of funding to research the underlooked and life-threatening diseases like RE. Such as Alternating Hemiplegia of Childhood, Landau-Kleffner Syndrome and even more chronic neurological conditions that go unnoticed, even when crucial for a child’s well being as well as development.

But with improved research for Pediatric Neurological conditions, we can make a difference in the lives of children worldwide. My hope for humanity is to advance research, specifically regarding rare neurological conditions that occur in children. In order to save the minds of future generations that could possibly save the world, we have to save them first.

DaVinci Surgical Robot By Edwin Feng

Abstract

Surgery has become one of the most known medical procedures in today's world, and every person at one point in their life will go through at least some sort of surgery, from surgeries that will help with your vision to some that will help prevent life threatening diseases.

Today, one main reason humans use surgical procedures is to contain diseases such as cancer and strokes, which is the second leading cause of death in the US. As surgical robots quickly gain popularity in our industry, we have to develop an understanding on how these bots are built and whether or not it's safe to implement these into our surgical procedures regularly. This can be done by acknowledging the potential risks and disadvantages these robots might have when performing a surgery operation versus a surgeon. One great example of current surgical robots in the market that we can look at is the Da Vinci robot, which is considered the "most advanced platform for minimally invasive surgeries", and also the most popular surgical robot till this date. By using the Da Vinci robot as an example, we are able to find limitations to the current surgical robots which allows us to understand how these limitations affect the potential of these robots.

While thinking about this, Edwin, with the guidance of his mentor, creates a complex model of one of these robots with an understanding of cost, efficiency, and adaptability, furthermore, making an analysis research paper to allow others to also understand the potential of automated surgical robots.

Introduction

Surgery could have many different uses such as glossectomy, and rhinoplasty, both of which you could say are not necessary to live a fulfilling life as a human. There are, however, important surgeries that everyone goes through in their lives, some of which are vital for our living. One example is cancer removal. Cancer has been the second leading cause of death globally, following up with cardiovascular diseases [1]. Although there are no direct cures for cancer, there are some important treatments that allow us to contain this disease, these treatments include radiation therapy, chemotherapy, and surgery. Surgery, however, doesn't always go according to plan because of the inconsistency of surgeons and accidentals. According to selective data, approximately 1 of 112,00 surgical procedures have errors that occur [3], which shows that trusting a surgeon could mean you have a small chance of your life being taken away. To fix this small amount of inconsistency, there has been a developing technology that we've been using, robotic surgery.

The start of robotic surgery dates back to the mid-1980s and the first surgical robot ever recorded to be implemented into surgical procedure was the PUMA 560[2]. As the development of surgical robots started to advance, it has become apparent that the distribution of thousands of these surgical systems has been revolutionary to global health care systems because of the millions of procedures being performed. One important topic to note is that the most popular

surgical robot in the market is the da Vinci robot which is developed by the US company, Intuitive. There are different da Vinci robots that could perform surgery on various parts of the body. To understand the making of surgical robots, we need to look at why the da Vinci robot is the most efficient one and whether or not every future surgical robot will be based on the DaVinci.

As we slowly accept these technologies to our societies, we need to pay close attention to their potential and how current surgical systems in the market will affect the future of surgical procedures. In order to understand the potential of these surgical procedures we first need to understand the factors that play into what makes a surgical robot reliable. How accessible is the robot to many parts of the globe? What is the cost of making these robots? What are the chances of technological failure when performing an operation with these robots? How could these robots adapt to our society?

Existing Robots

The history of robots in general dates back to the early 1950s by George C. Devol, an American inventor which created the "world's first industrial robot". As an inventor of an industrial robot, it was unfortunate for him that he wasn't able to succeed in selling his robot on the market. However, in the late 1960s, Joseph Engleberger, a businessman and engineer, founded his company called "Unimation" that was able to modify and market Joseph's invention which started the spark of robotics. [4] Not long after the invention, the idea of surgical robotics was brought up in the mid-1980s. The term surgical robot or Robotic-assisted surgery is a process where a surgeon uses controls through a GUI (Graphical User Interface) and conducts surgery using instruments translating surgeon's movements that performs precise incisions in your body.

Today, the most common surgical robot that is commonly referred to in the medical engineering community is the da Vinci robot made by the company, Intuitive. The da Vinci is not just a specific robot that was developed and marketed in various of the world, it is a surgical system with different variations of the robot that helps perform multiple tasks including cardiac, urologic, gynecologic, and pediatric surgery, which will help with prostate cancer. According to Uchealth, three out of four patients with prostate cancer had surgery performed using the da Vinci surgical robot in the U.S, which shows how our society is quickly trusting these technologies that was just recently implemented into our society.

The reason why the da Vinci robotic system was so special was because of how it was instantly trusted by the FDA. The FDA, US Food and Drug Administration is a federal government agency of the department of health and they're responsible of ensuring the safety of medical devices. The da Vinci robotic system was first made at the Leipzig Heart Center Germany in 1998. Not long after, it was the first robotic system to gain FDA approval for general laparoscopic surgery which meant that it was commercially available in the United States.

Laparoscopic surgery, an invasive surgical procedure that gives a surgeon access to a patient's abdomen and pelvis without making large incisions, is the most successful subfield of

medical robots. Through multiple developments of the da Vinci, there are now offers not only laparoscopic, but also offers endoscopic surgery and more than 50 different instruments have been released. The da Vinci robot has 3 components to it, the control console, a vision cart, and a surgical robot's manipulator arm unit. The control console is a vital part of the da Vinci robot since it is operated by a surgeon, but instead of imitating the surgeon's exact movements, the robot translates those movements to what best fits the situation (going through millions of safety checks in the process). The control console consists of two controller arms and a foot panel as well as a console where the surgeon has 3d vision of the patient. The vision cart is a high definition 3d vision system that gives direct feedback and an overview of the patient that holds the endoscope. And finally, the arm unit which of course is how the surgical gets performed. Although people may say the da Vinci surgical system is already the most developed version, Intuitive have plans on future additions to the robots. These three goals include enhanced imaging, intelligent systems, and less invasive approaches. This includes the recently developed da Vinci's Xi new and improved endoscopy, a procedure (usually involving a tube equipped with a camera going down your throat) that allows a surgeon to examine your stomach. This new procedure is called "docking" which is facilitated by lasers which allows the robot to find the optimal position to perform surgery on.

The use of the da Vinci robot or any surgical robots like Hugo, for example, have some risks and drawbacks. Even though robotic surgery is more precise than open surgery and has a far more success rate. There are still times where there are robotic malfunctions which can end up with broken pieces ending up in patients that can possibly burn their tissues. Or a sudden power outage mid-operation which could be life threatening [8].

Potential for Future Robots

To understand how these robots are built, we need to break down the robot into several pieces. Firstly, the part where the surgeon does the controlling is called the Master Tool manipulator and is made with two joysticks using motion sensors and button switches that allows the system to send signals to the robot on what the surgeon wants to do. While controlling the robot, the surgeon needs to able to see what's happening with the patient which is what the camera and the endoscopy on the arm does. The built in GUI screen is inside the robot and the only way to view it is through a small glass screen which turns on when there is a face triggers the motion sensors. The last part of the surgeon console is the foot panel, where you could change your camera angle and operate with the other 2 arms that you have access to.

Although the overall success rate of robotic surgery isn't stated as clear as overall surgery success rate. It is stated that a published data of the Da Vinci surgical system pyeloplasty which showed success rate of 94% to 100%. [12] Pyeloplasty is a procedure done when the urine is pushed to the kidney which causes kidney infections. Although this doesn't correlate that well with cancer removal, this still gives us a general range on how successful this surgical system is. At the time when these operations do "fail", those failed operations also get another operation which is shown with a success rate of 78% and 94%, which goes to show how these robots are

precise. So it's safe to say that they are indeed able to be consistent if not more consistent than open surgical procedures and they will therefore be implemented in future hospitals.

Some important "EndoWrist SP Instruments" from the da Vinci Surgical systems are often crucial to the procedure process such as graspers, scissors, and needle drivers. It also includes unique distal tip designs which allow the robot to have a greater range of motion in which a human can't do. What isn't clear is if the da Vinci robot is able to configure different instruments. There does seems to be configuration methods but these often require a whole arm that isn't completely necessary when it comes to performing the surgery. One way to make the da Vinci Surgical System more accessible is to make the robot to allow small instrument add-on's in order to change the type of procedure you are performing. This is one method to make the robot less costly and more accessible to other hospitals.

Instruments for the patient cart isn't the only factor that will increase the adaptability of the robot but there could also be changes to the vision cart. It allows other surgeons to monitor the procedure while sending signals from the surgeon console to the patient cart. This can be compared to pc's. When people want to have high quality/definition visuals, there needs to be an external computer that isn't built into the monitor. Why exactly aren't computer components built into the monitor? It's because the monitor is simply too small. The vision cart acts like a pc where it sends signals to give high definition visuals. However, the surgeon console is big enough to have the vision cart parts implemented into it. This one method would allow a whole part of the da Vinci robot to reduced into two parts which overall can reduce the price and increasing the potential for these robots to be implemented in the future.

Discussion

Throughout the years it's clear that Surgical Robots have become revolutionary. One big example is the da Vinci Surgical System as it's the first surgical robot to be approved by FDA. From the first commercial sale in Leipzig Heart center in Germany to over 2344 surgical systems distributed across the US. Although it has some risks involving instrument malfunctions, bleeding, infection, scarring, and having gas/air trapped beneath the skin. With these drawbacks, however, there are many advantages where there are magnified vision systems for surgeon view, higher range of motion that can't be done in an open surgery, and a huge laparoscope. To summarize those 3 benefits, it basically means it's more precise and gives more information. The potential for these robots are limitless as there's still many surgical robots that are in development and are hoping to become more accessible to the outside world.

Conclusion

Over the years of da Vinci Surgical system development, there have been many different changes to the robot making it more advanced which makes it easier to use. The different parts of the surgical system allow us to understand the cost and how it could be available to other countries. The da Vinci surgical system consists of 3 different parts: the patient cart, the vision cart, and the surgeon console. These different parts allow the robot to make high-definition

visuals allowing the surgeon to produce precise surgery on the patient. The precision of the surgical robot and the consistency allows this surgical system to become revolutionary. However, to make them more accessible to other countries, there should be tweaks in combining the design to be able to market it in less fortunate countries that might need these technologies.

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Review of the Potential of Microbiome Research: Shifting Paradigms in Understanding Human Health By Yuechen Wang

Abstract

Recent research and implications in the field of microbiome science for human health and the latest advancements and discoveries have revealed to us with a new understanding of the microbiome has transformed our perspective on the interplay between microbes and human physiology. This article will further explore and illustrate the potential applications of microbiome-based interventions in personalized medicine, and the challenges that lie ahead.

Introduction

The human body is not considered an isolated entity, instead is recognized as an intricate ecosystem teeming with microorganisms. The collective genetic material of these microbial communities, known as the microbiome (Microbiome, n.d.), has emerged as a captivating field of research that is revolutionizing our understanding of human health. Here, we explore recent advancements in microbiome research and shed light on the complex relationship and interplay between microbes and human physiology.

The Microbiome: A Complex Ecosystem

The human microbiome is a vast collection of microorganisms residing in and on our bodies, primarily in the gut, skin, and mucosal surfaces (Microbiome, n.d.). These microbial communities are diverse, with bacteria being the most abundant members. Recent research has revealed that the microbiome plays a crucial role in maintaining human health and homeostasis (Ogunrinola et al., 2020). The microbiome contributes to digestion, vitamin synthesis, and metabolism, while also playing a pivotal role in immune system development and protection against pathogens (Ogunrinola et al., 2020). The emerging understanding of the microbiome-host interaction highlights the intricate relationship between microbial communities and their human hosts.

Traditional Paradigms in Understanding Human Health

A. Germ theory and the focus on pathogens:In the history of medicine, the emergence of germ theory was a groundbreaking paradigm shift. Germ theory, pioneered by Louis Pasteur and Robert Koch, proposed that many diseases are caused by specific microorganisms, known as pathogens. This theory revolutionized our understanding of infectious diseases and laid the foundation for modern healthcare practices (Koch, 1884; Pasteur, 1861).

Under the germ theory paradigm, the primary focus of healthcare became the identification and eradication of pathogens. This led to significant advancements in disease control, such as the development of vaccines to prevent viral and bacterial infections. Antibiotics also became a powerful tool in treating infectious diseases by targeting and eliminating specific pathogens.

B. Reductionist approach to studying diseases: Another traditional paradigm in understanding human health is the reductionist approach. This approach involves breaking down complex systems into smaller, more manageable components to study and analyze. In medical research, reductionism has been widely employed to identify isolated factors in disease causation and develop targeted treatments.

The reductionist approach has yielded valuable insights into human health. By studying individual genes, proteins, or cellular processes, scientists have been able to uncover important mechanisms underlying diseases and develop specific interventions. This reductionist approach has played a crucial role in advancements like targeted cancer therapies.

However, the reductionist approach also has its limitations. It tends to oversimplify the complexity of biological systems, as diseases often involve intricate interactions between various factors. This approach may overlook the interconnectedness of different bodily systems and fail to capture the full picture of disease development and progression.

C. Limited understanding of the complexity: Germ theory and reductionism, in previous studies, made significant contributions to medical knowledge but were revealed to possess only a meager comprehension of the intricacies of human-microbiome interactions. The human microbiome, teeming with trillions of microorganisms inhabiting and enveloping our bodies, had long been disregarded or merely viewed as a passive observer in matters of human health.

However, recent scientific breakthroughs have illuminated the pivotal role of the microbiome in sustaining overall well-being. The microbiome functions as a vibrant ecosystem, engaging with the human host in convoluted manners. It exerts influence over diverse physiological processes, encompassing digestion, metabolism, and immune response (Sender et al., 2016).

Traditionally, disruptions in the microbiome were primarily attributed to infectious diseases caused by pathogenic microorganisms. Nevertheless, emerging research has established connections between imbalances or modifications in the microbiome and a wide array of diseases and conditions, stretching far beyond infectious ailments. For instance, dysbiosis, an imbalance in the gut microbiome, has been associated with inflammatory bowel disease and allergies (Gensollen et al., 2016; Arrieta et al., 2015).

Understanding the complexity of human-microbiome interactions poses significant challenges. The microbiome is highly individualized, shaped by factors such as genetics, diet, lifestyle, and environmental exposures. Moreover, the dynamic nature of the microbiome requires advanced tools and techniques to comprehensively analyze its composition and functions (Yatsunenko et al., 2012).

In light of these limitations, the shifting paradigms in microbiome research are challenging traditional notions of human health. By recognizing the microbiome as an essential component contributing to human health, researchers are able to reveal and further explore the complex relationship between them.

Recent Research Findings

In recent years, significant studies were conducted in microbiome research where our understanding of its impact on human health is reshaped. Studies have revealed the influence of the microbiome on immune system development and function. For instance, a study published in Cell by Chu et al. (2016) demonstrated that specific gut bacteria promote the development of regulatory T cells, which are crucial for immune tolerance and preventing autoimmune diseases. This finding highlighted the role of the microbiome in shaping the immune system and its potential implications for autoimmune disorders.

Findings from another study suggest a link between mental illness and the gut microbiota. A study by Cryan and Dinan (2012) on the "gut-brain axis" examined bidirectional interactions between gut microbes and the brain and went on to show the relationship between gut microbes and mental health (Liu et al.). Microbes in the Gut Neurotransmitter Synthesis It have been found to alter and influence mental health and behavior. The unearthing of the correlation between the microbiome and mental health conditions, such as anxiety, depression, and autism spectrum disorders, has unfurled a captivating new realm of investigation. It's enthralling to witness how our gut microbiome can exert influence on our mental well-being.

Furthermore, a study conducted by Turnbaugh et al. (2006) and the author furnished evidence bolstering the connection between the gut microbiome and metabolic factors like obesity and type 2 diabetes. This implies that the bacteria dwelling in our gut can partake in our weight management and overall metabolic health. Recent research has even illuminated how these minuscule organisms impact pivotal aspects such as adipose tissue function, insulin sensitivity, and energy regulation. It's mind-boggling to contemplate the origins of these processes and how they are swayed by the microbiome.

All these revelations, in conjunction with myriad other recent studies, have underscored the profound significance of the microbiome. They unveil its potential as a promising target for concocting therapeutic interventions to augment our overall well-being. It's an exhilarating era in the realm of microbiome research as we persist in unraveling the intricate and mesmerizing interplays between our corporeal forms and the microbial world within us.

Microbiome and Personalized Medicine

The growing understanding of the microbiome has paved the way for personalized medicine approaches that leverage the microbiome as a diagnostic and therapeutic tool. Researchers have identified specific microbial signatures or patterns associated with various diseases, offering potential microbiome-based diagnostics and biomarkers. For example, a study published in Science Translational Medicine by Zackular et al. (2016) identified distinct microbial signatures in patients with inflammatory bowel disease (IBD) and colorectal cancer. The researchers found that the gut microbiota could serve as a potential non-invasive diagnostic tool for these conditions, providing valuable insights for early detection and risk assessment (Zackular et al., 2016).

Furthermore, targeted therapies based on manipulating the microbiome are being explored. Fecal microbiota transplantation (FMT), which involves giving a patient feces from a donor who is healthy, (Vindigni and Surawicz), has shown promising results in treating recurrent Clostridioides difficile infection (CDI). A study published in The New England Journal of Medicine by van Nood et al. (2013) demonstrated the efficacy of FMT in resolving CDI symptoms and restoring the gut microbiota. This approach has revolutionized the treatment of CDI and highlighted the therapeutic potential of modulating the microbiome (van Nood et al., 2013).

Scientists are delving into the realm of microbial-based therapeutics, exploring probiotics and engineered bacteria as potential remedies to restore microbial equilibrium and enhance health outcomes. A striking illustration of this lies in a groundbreaking study conducted by Sonnenburg and Bäckhed (2016) and published in Science Translational Medicine, which unveiled auspicious findings in the realm of averting and addressing antibiotic-associated diarrhea (AAD). These examples demonstrate the potential of precision modulation of the microbiome for tailoring treatments to individual patients and optimizing therapeutic efficacy (Sonnenburg & Bäckhed, 2016).

Challenges and Limitations

While microbiome research offers promising avenues for understanding and improving human health, it also presents challenges and limitations. The complexity of the microbiome and its interactions with the human host make the analysis and interpretation of microbiome data challenging. Variations in study design, sample collection, sequencing methods, and data analysis tools contribute to inconsistencies and difficulties in comparing results across studies. Standardization of methodologies and data-sharing initiatives, such as the Human Microbiome Project, are crucial for addressing these challenges and ensuring the reliability and reproducibility of microbiome research.

Additionally, ethical considerations surrounding the manipulation of the human microbiome warrant careful examination. Questions regarding safety, long-term effects, and unintended consequences of microbiome interventions need to be addressed to ensure responsible and ethical use of microbiome-based therapies.

Retrospective Studies

The purpose for conducting retrospective research is to gain an in-depth understanding of the long-term impact of the microbiome on human health. A retrospective study published in Cell Host & Microbe by Vatanen et al. (2018) examined the gut microbiota of individuals before and after the development of type 1 diabetes. Significant changes in microbial composition and projected functional pathways were discovered by the researchers, pointing to a possible connection between the microbiome and type 1 diabetes development (Vatanen et al., 2018).

Another retrospective study published in JAMA Network Open by Suez et al. (2019) investigated the association between long-term antibiotic use during childhood and the development of obesity in adulthood. The researchers analyzed the health records of individuals and compared the antibiotic exposure history with body mass index (BMI) measurements. The study revealed a positive association between antibiotic accumulation and risk of obesity, drawing attention to the potential long-term consequences of antibiotic-induced effects on the microbiota (Suez et al., 2019).

Translating Research into Practice

Translating microbiome research into clinical practice requires navigating regulatory considerations and safety assessments. Regulatory agencies around the world are beginning to recognize the importance of microbiology and are working to establish guidelines for their development and use. Rigorous clinical trials and robust evidence are essential for gaining regulatory approval and ensuring patient safety.

Furthermore, interdisciplinary collaboration among biologists, clinicians, bioinformaticians, and regulators is essential to successfully translate microbiological research into clinical practice. Open dialogue and knowledge exchange among stakeholders will help address challenges and foster innovation in the field.

Future Directions and Opportunities

The field of microbiome research holds vast untapped potential. Further investigations are needed to explore uncharted frontiers such as the lung and oral microbiome and their impact on health and disease. For instance, a study published in Cell Host & Microbe by Segal et al. (2016) revealed distinct microbial communities in the lung microbiota of patients with chronic obstructive pulmonary disease (COPD). Understanding the role of the lung microbiome in respiratory disorders could lead to novel diagnostic and therapeutic approaches (Segal et al., 2016).

In addition, understanding the role of the microbiome in personalized nutrition and preventive healthcare can pave the way for tailored dietary interventions that optimize individual health outcomes. Recent studies, such as a review published in Cell Host & Microbe by Sonnenburg and Bäckhed (2016), have highlighted the importance of considering the interplay between diet, the microbiome, and host metabolism in developing personalized nutrition strategies.

Continued research, funding, and collaboration are essential to unlock the full potential of the human microbiome and harness its therapeutic benefits for improved patient care.

Conclusion

In conclusion, remarkable advances in microbiological research have transformed our understanding of human health and disease. The microbiome is now recognized as an important determinant of our well-being, affecting aspects of human physiology and health despite it was

once overlooked. Recent research findings have provided strong evidence for the impact of microbiota on immune development, mental health, and metabolism. These advances have changed paradigms in our understanding of human health, highlighting the complex relationship between microbial communities and their human hosts

The potential of the microbiome in personalized medicine is vast. Researchers have identified specific microbial signatures associated with diseases, offering opportunities for microbiome-based diagnostics and biomarkers. By analyzing the composition and diversity of the microbiome, clinicians can gain valuable insights into disease states and predict treatment outcomes. Moreover, targeted therapies based on manipulating the microbiome, such as fecal microbiota transplantation (FMT), have shown remarkable success in treating conditions like recurrent Clostridioides difficile infection (CDI). The ability to restore microbial balance through precision modulation of the microbiome opens new avenues for therapeutic interventions tailored to individual patients.

Despite the promising advancements, challenges, and limitations exist within the field of microbiome research. Standardization of methodologies and data analysis tools is crucial for ensuring consistency and reproducibility across studies. The complexity of the microbiome, coupled with variations in study design and sample collection, necessitates rigorous scientific protocols. Moreover, ethical considerations surrounding the manipulation of the human microbiome, including safety concerns and unintended consequences, must be carefully addressed to ensure the responsible and ethical use of microbiome-based interventions.

Translating microbial research into clinical practice requires collaboration among researchers, clinicians, bioinformaticians, and regulators. Guidelines and regulations for the development and implementation of microbial-based therapies must be established to ensure patient safety and efficacy. Ongoing interdisciplinary collaboration and knowledge exchange are essential to navigate the challenges and drive innovation in this rapidly evolving field.

Looking ahead, the future of microbiome research holds tremendous promise. Exploring uncharted frontiers such as the lung and oral microbiome will provide further insights into the impact of the microbiome on human health and disease. Understanding the interplay between the microbiome, diet, and host metabolism will enable the development of personalized nutrition strategies that optimize individual health outcomes. Continued research efforts, funding support, and collaboration are pivotal to unlocking the full potential of the human microbiome and harnessing its therapeutic benefits.

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The Implementation of CRISPR-Cas9 to Address California's Almond Economy and its Effects By Pranav Rajapu

Abstract

The relatively new development of the CRISPR-Cas9 gene editing technology, which was adapted from a naturally occurring immunological system in prokaryotic bacteria, has significantly transformed a variety of scientific disciplines, ranging from cell and gene therapy to biofuel production. This review will first consider the process and adaptation of CRISPR-Cas9 technology. It will review the process of designing a single guide RNA (sgRNA) to purposefully introduce a modification in a target organism. It will also review several genes of interest that can be introduced by CRISPR technology in the context of *Prunus dulcis* (almond plant). Following this study will be an exploration of the implications of these genes of interest and CRISPR-edited almond plants with regards to their potential benefits in the state of California and its almond economy.

Introduction

The almond tree is native to Southwest Asia, especially the Levant region, but is currently produced primarily in California. In fact, California is responsible for producing 80% of the world's almond supply and 100% of the commercial supply of the U.S. It is also worth mentioning that there are two main varieties of *Prunus dulcis*: the typical sweet almond (*Prunus dulcis* variety *dulcis*), which will be the primary focus of this review, and the bitter almond (*Prunus dulcis* variety *amara*). Almonds have many uses in foods and topical application: they may be consumed as raw, blanched, or roasted nuts, they are often incorporated into confectionery foods, marzipan, and meat, poultry, fish, and vegetarian dishes, and they are also used for the extraction of almond oil (used for skin treatment). Almonds are also rich in sources of nutrients and proteins. However, one major limitation of almond tree growth is that they only grow best in Mediterranean climates with dry summers and mild/wet winters, making them unsuitable for growth in other parts of the United States. Furthermore, almond trees are especially susceptible to spring frosts, which can drastically reduce yield (Grant). Almond trees also require great amounts of nitrogen to synthesize its component proteins and nutrients, with many growers reporting that they added around 1 kg of nitrogen per tree annually ("Almond Tree Fertilization"). These problems, along with other agricultural issues, are some of the main focuses of genetic engineering technology.

CRISPR-Cas9 technology has recently emerged as a breakthrough biotechnology with many potential implementations throughout various scientific disciplines. It was originally adapted from a naturally occurring bacterial immunological defense system that was intended to protect against damaging viruses. In this bacterial process, bacteria would identify and insert segments of the viral DNA into their own DNA to form special patterns known as CRISPR arrays. Using these arrays, the bacteria could then synthesize special RNA sequences to attach to similar invading viruses and then "cut" the DNA of these viruses using an endonuclease such as

Cas9. This naturally occurring process was modified into the present gene editing technology by creating special guide RNA sequences, whose purpose is similar to the RNA sequences derived from the CRISPR arrays. The guide RNA would bind to both the targeted DNA sequence as well as the Cas9 enzyme. Thus, the guide RNA would "guide" the Cas9 enzyme to the particular region of DNA and induce a cleavage such that it can be removed or replaced with new genetic information and allow for genetic modification ("What Are Genome Editing and CRISPR-Cas9?"). More specifically, the induced cleavage is caused by a nuclease (such as Cas9) that introduces a double-stranded break in the DNA that can then be repaired by cellular mechanisms. Of these cellular mechanisms, there is the more error-susceptible non-homologous end-joining (NHEJ) mechanism and the more precise and commonly-used homology-directed repair (HDR) mechanism. In the NHEJ mechanism, broken ends of DNA are attached to each other, frequently resulting in insertion and deletion (indel) mutations. Meanwhile, the HDR mechanism uses the homologous guide sequence to intentionally introduce a specific sequence (Miyaoka et al.). In summary, repair mechanisms can create mutations in the target region that may interrupt, eliminate, or correct defective genes. There are two major pathways of CRISPR gene editing: gene knock-out and knock-in. When the nuclease removes DNA sequence and causes an indel mutation to stop expression of the gene, it is referred to as gene knockout. When a new gene sequence is introduced into the newly cleaved region (such as via the HDR mechanism), it is referred to as gene knockin ("Gene Knockout: IDT").

Overall, CRISPR-Cas9 has garnered much attention recently for its convenience and efficiency in genetic engineering of many organisms (Rodríguez-Rodríguez et al.). Because it allows researchers to "correct errors in the genome and turn on or off genes in cells and organisms quickly, cheaply and with relative ease," this technology "has a number of laboratory applications including rapid generation of cellular and animal models, functional genomic screens and live imaging of the cellular genome." Indeed, it has already been employed in mice to repair defective DNA and cure genetic disorders, clearing a path to CRISPR-Cas9 usage in other research aspects and even in humans, with potential applications including gene therapy as well as HIV and cancer treatment (Redman et al.). One major implementation for this technology is in agriculture, where it can be used to confer novel traits and resistances to plants and crops. This comes at a unique time as breeders and scientists are collaborating to meet an increasing global food demand, which is being hindered by plant diseases and climate change. However, the advent of CRISPR-Cas9 technology has enabled scientists to engineer traits for crop improvement with the aid of precise genome editing and transgene-free applications (Zaidi et al.). Already, it has been involved in genome editing in "41 food crop species, 15 industrial crops, 6 oil crops, 8 ornamental crops, 1 fiber crop and feed crop" to improve crop quality based on "physical appearance, edible quality, fruit texture and nutritional value" (Liu et al.). Some CRISPR-engineered crops, such as browning-resistant mushrooms, high-amylopectin waxy corn, and false flax with enhanced omega-3 oil, have even been approved by the US Department of Agriculture in record time. As demonstrated by these USDA-approved crops, plant breeding technologies such as CRISPR-Cas9 hold great promise for engineering the crops of the future

due to their precision and efficiency (Zaidi et al.). In particular, this review will consider how CRISPR-Cas9 technology can genetically modify *Prunus dulcis* (almond plant) to confer biotic and abiotic traits. Following this section will be an introduction to certain genes of interest that could be inserted using the CRISPR-Cas9 genetic engineering technology to confer traits to address these problems as well as enhance other aspects of almond tree growth, such as water requirements, amount of seed oil present, and others. Some of these potential genetically engineered changes will affect genes already present in the almond tree genome, while others will introduce new gene sequences.

Designing a sgRNA

During experimentation, a single guide RNA (sgRNA) can be used to direct the Cas9 nuclease (enzyme that cleaves nucleic acids) to a specific DNA target sequence in the almond genome to study the effects that that gene has towards specific desired traits. In this case, we will consider the SRO1 gene from *Zea mays* (corn) and a genetically similar gene from the *Prunus dulcis* plant named ALMOND_2B029448 that encodes for Poly [ADP-ribose] polymerase (PARP). This example will use the Px330 plasmid as the vehicle for RNA insertion, as depicted in Figure 1. First, the forward guide sequence for the protospacer adjacent motif (follows DNA region for cleavage) is generated based on the target sequence ALMOND_2B029448 gene: TCTCTGAGAGAGGAAGAACT. This guide is a stretch of the original gene sequence that reads 5' to 3'. Then, other plasmid reconstruction nucleotides can be added to the 5' end of the guide to generate the forward primer. The complementary reverse primer, which will also read 5' to 3' but in the opposite direction at the plasmid site, can also be generated with other plasmid reconstruction nucleotides. Essentially, what was done was that the sgRNA was manufactured such that it contained the genetic information of the ALMOND_2B029448 gene. This single-stranded sequence was then made into a double-stranded sequence by adding the complementary strand to the sgRNA. The restriction enzymes XbaI and KpnI then cleave the region between them, which opens up the Px330 plasmid. The double-stranded forward and reverse primers, consisting of the sgRNA and its complementary strand, are then inserted into the double-stranded Px330 DNA plasmid, which serves as the vehicle to introduce the sgRNA to the organism. The Px330 plasmid will also have the Cas9 enzyme inserted. The resulting plasmid with the sgRNA insert is depicted in Figure 2. As a side note, during experimentation, restriction enzymes can also be attached to either end of the sgRNA insert such that if the desired phenotype is not observed, this particular sgRNA can be replaced with another sequence instead.

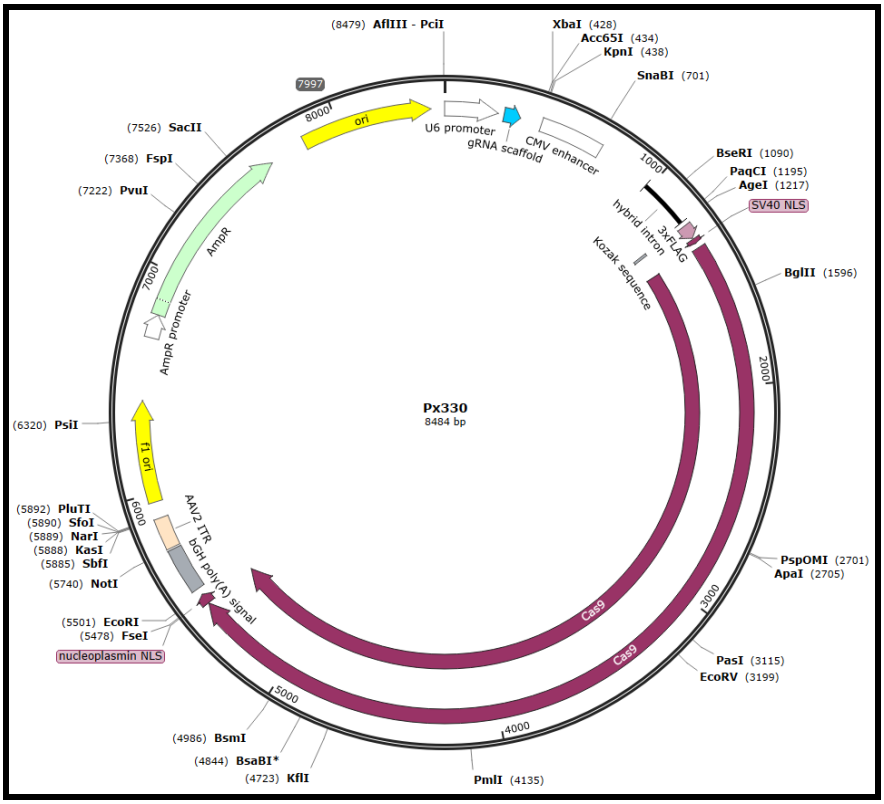

Figure 1: Px330 plasmid before insertion of sgRNA

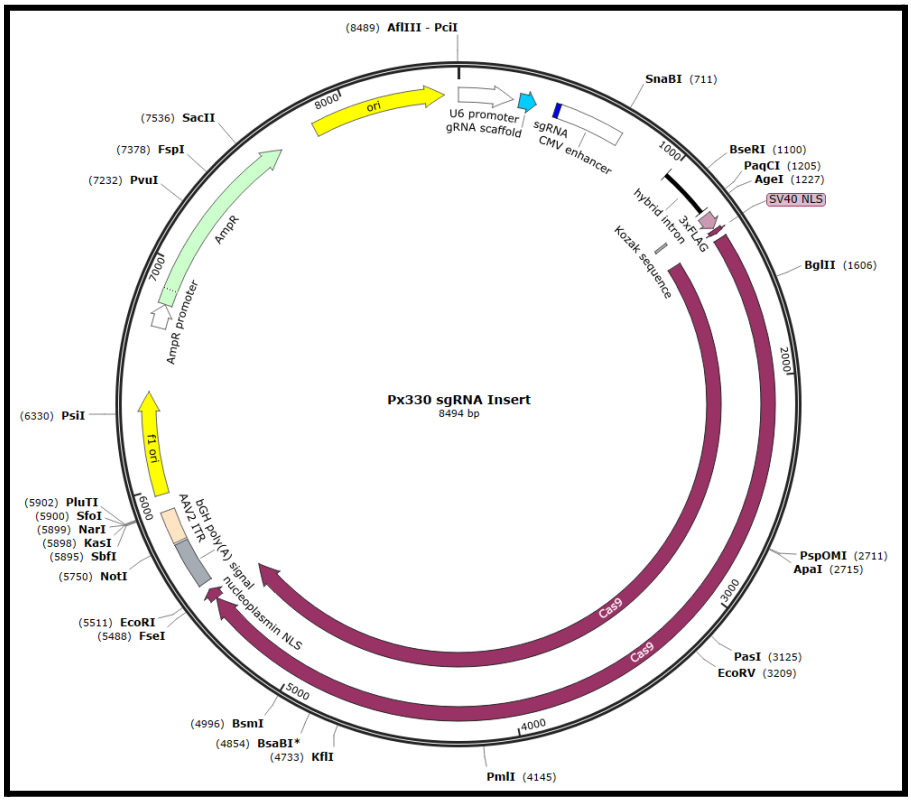

Figure 2: Px330 plasmid after insertion of sgRNA (see region after gRNA scaffold)

Since the plasmid can be inserted into the cell, if the cell replicates during cell division, the sgRNA will still be present in the new cell. Restriction enzymes can then be introduced to cleave the plasmid at the ends of the region containing the sgRNA. During this experimental process, the temperature can be raised to disrupt the bonds of this region, such that the sgRNA and its complementary strand can be separated. Once identified, the sgRNA can then attach to the expressed Cas9 nuclease. This newly-formed complex, using the complementary sgRNA to bind to the ALMOND_2B029448 gene target sequence, can then cleave the DNA at that region. In its place, the SRO1 gene can be introduced into the genome to replace the newly cleaved sequence via the HDR mechanism, using a template to add the appropriate nucleotides for the SRO1 gene. Either end of the newly-introduced gene will also contain the same nucleotides as the original strand that was cleaved (allows it to fit in with the organism's genome). While in this scenario the gene was entirely replaced by the SRO1 gene, it may also be mutated to make it more similar to the SRO1 gene instead of entirely replacing it. Finally, the phenotype of the almond must be observed to examine how the plant behaves and determine whether the desired trait was conferred or not.

Typically, this process of designing a sgRNA and cleaving the target DNA sequence must be repeated multiple times during experimentation because the phenotype of the modified gene must be examined to verify if they are the same in both the original plant (*Zea mays*) as well as in *Prunus dulcis*. After all, the target sequences are suggested starting points from homologous genes from other experiments, but ultimately, the conferring of the desired trait can only be achieved through experimentation. If genetically engineering the target sequence does not provide the desired trait, researchers may observe the network of how this particular gene works in a pathway, and then conduct experiments on other genes in the pathway. If this also does not yield any results, experimentation would have to proceed on various other areas of the genome. It is also important to note that a desired trait is often given by multiple proteins, so conferring such a trait to a new organism may require multiple areas of cleavage and genetic changes, as well as multiple experiments. Furthermore, according to Ricroch et al., "heritability and the transgene-free character of the generated plants were demonstrated in several studies," indicating that if a desired gene is introduced into a plant and successfully confers the desired trait, the progeny should also exhibit said characteristics, allowing for many new implementation perspectives in agriculture and such (Ricroch et al.).

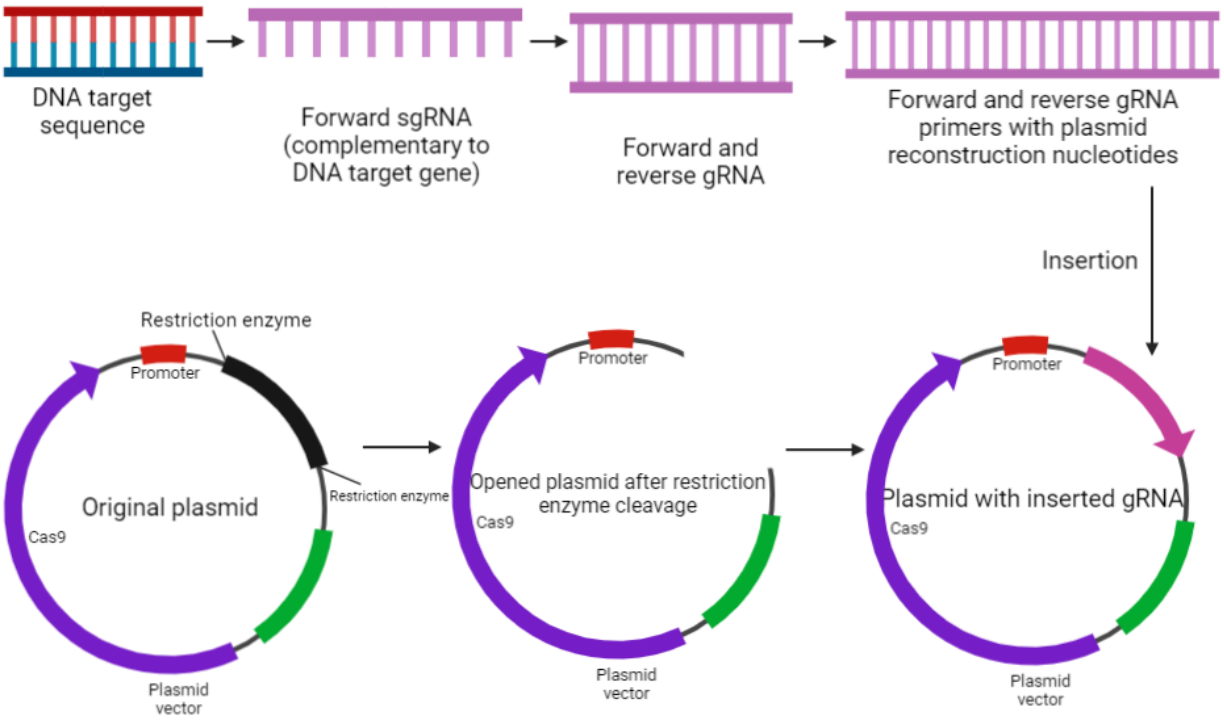

Figure 3: Designing a sgRNA and inserting it into a plasmid

Genes of Interest

CRISPR gene editing technology has already been implemented on certain common plants to modify genes and confer desired traits. Many of these experiments incorporate gene knockouts using Cas9 and gRNA, in which a gene sequence is made inactive by genetic engineering processes, as previously mentioned. This section will identify possible genes of interest and how their insertion into the *Prunus dulcis* plant via the aforementioned process of CRISPR and knockout and/or knockin can confer various desirable traits and phenotypes. A CRISPR knockin can in theory either build upon a knockout—by introducing a new gene sequence in the cleaved region—or by randomly inserting a new gene sequence into the new genome.

The first gene of interest is the SRO1 gene. According to a study of this gene in maize, "three non-synonymous variants in a drought-resistant allele of ZmSRO1d-R resulted in plasma membrane localization and enhanced mono-ADP-ribosyltransferase activity of ZmSRO1d toward ZmRBOHC, which increased reactive oxygen species (ROS) levels in guard cells and promoted stomatal closure. ZmSRO1d-R enhanced plant drought resilience and protected grain yields under drought conditions, but it led to yield drag under favorable conditions" (Gao et al.). The SRO1 gene was thus involved in plant resilience and protected grain yields under drought conditions. In terms of its application to the almond plant, the SRO1 gene can be introduced via CRISPR/gRNA plasmids to a homologous sequence to study its effects on the almond plant drought resilience. This trait could hold a host of benefits for almond plants, which have high water demands, because they would be better adapted to grow in drier climates, especially in

times of climate change and more severe weather. The possible consequences of making almond plants more drought resilient in California will be further explored in a later section.

Another gene of interest is the fatty acid desaturase 2 (FAD2) gene, which encodes the enzyme of the same name. In a study of this gene in the *Camelina sativa* plant, "selective, targeted mutagenesis of the three delta-12-desaturase (FAD2) genes was achieved by CRISPR-Cas9 gene editing, leading to reduced levels of polyunsaturated fatty acids and increased accumulation of oleic acid in the oil" (Morineau et al.). The results of this study suggest possible insight into the function of the FAD2 enzyme: to insert a double bond at a certain position of oleic acid to obtain linoleic acid. It also catalyzes the biosynthesis of polyunsaturated fatty acids, such as linoleic acid, from monounsaturated fatty acids, such as oleic acid. In this study by Morineau et al., when the FAD2 sequence was targeted in the *Camelina sativa* plant, the following phenotypes were observed: there were reduced levels of polyunsaturated fatty acids and increased amounts of oleic acid, which enhanced the fatty acid composition of the seed oil (Morineau et al.). Thus, the results of this study suggest that the FAD2 gene is heavily linked with oleic acid oil enhancement in the accumulation. With respect to implementation in the almond plant, homologous sequences of the FAD2 gene can be targeted for inactivation by gene knockout techniques (involving Cas9/gRna plasmids) and replaced by the FAD2 gene. The phenotype of the almond plant could then be observed to study whether it has the desired effect of enhancing seed oil composition. An increased yield of almond oil can be beneficial from a commercial perspective because more almond oil can be extracted per almond, allowing for more efficiency in that industry.

The next genes of interest include two genes that are similar for the purpose of this review, named DGAT1 and PDAT1. Two researchers conducted experiments on the *Camelina sativa* plant to study endogenous biosynthetic pathways. According to their study, "by using a carefully designed guide RNA identical to all three homeologs, we demonstrate the ability of the CRISPR/Cas genome editing system to introduce mutations in all three CsDGAT1 or CsPDAT1 homeologous genes important for triacylglycerol (TAG) synthesis in developing seeds" (Aznar-Moreno and Durrett). Furthermore, "seed harvested from both CsDGAT1- and CsPDAT1-targeted lines was often shrunken and wrinkled," suggesting that (along with lipid analysis) "many lines produced seed with reduced oil content and altered fatty acid composition, consistent with the role of the targeted genes in seed oil biosynthesis" (Aznar-Moreno and Durrett). In other words, the results of the study demonstrate that these genes are heavily linked to the synthesis of triacylglycerol, which is very dense and contains high amounts of energy. This is especially significant because if this gene is introduced into the almond genome, an increased yield of triacylglycerol would be advantageous from an energy perspective because the almond plant's supply of these energy-dense molecules can be harvested for biofuel, providing a sustainable source of energy. Although it may not be immediately practical, as the world shifts away from fossil fuels and toward more renewable energy sources, these enhanced almonds can contribute valuable biomass to the energy production mix of the nation.

Consequence of Modified Almonds to the State of California

A consideration of the use of CRISPR-Cas9 in the state of California may be warranted due to its thriving almond economy. As the number one grower of almonds in the United States, California accounts for 80% of the world supply of almonds as well as the entirety of the domestic almond supply, and it generated $5.1 billion in exports in 2015. Clearly, the production of almonds plays no small role in the economy of California. However, as vital to the economy as they may be, almond plants require a notoriously large amount of water to grow in the Mediterranean climate of California. Requiring up to 4 inches of water every 2 weeks and a total of about 1900 gallons per pound of almonds, these plants are highly demanding and may die off if their water needs are not sufficiently met ("How Much Water Do Almond Trees Need?"). According to a 2017 study of the water-indexed impact of California almonds, each one has a "water footprint" of 12 liters (3.2 gallons) on average (Fulton et al.). Furthermore, a popular article published by Mother Jones in 2015 also reveals how California almond plants are notorious for consuming more than two billion cubic meters of water—significantly exceeding the amount of water consumed by the entire city of Los Angeles (Lurie).

Even more concerning is the ongoing climatic conditions in the California region: droughts. The deadly droughts have limited overall water availability, exacerbating the disproportionate water consumption of one of California's most extensively irrigated crops and threatening its production. Since little water is available due to the droughts, almond planters deplete reservoirs and pump more and more groundwater, placing further strain on already limited water supplies. This, in turn, results in shrinking water availability in the region. In fact, according to the "2022 Annual Water Supply and Demand Assessment Summary Report" published by the California government, seventy-three out of four hundred fourteen water agencies surveyed reported that they would not be braced to meet water demands for the following year if they did not implement response action, while three additional agencies reported that they would not meet water demands regardless of any response action taken ("2022 ANNUAL WATER"). This endangers the survival and wellbeing of the regions and industries that those agencies are responsible for. Even beyond the drought conditions, global warming presents another threat to water availability for almond plants. As climate change continues to exert its influence, severe droughts are likely to continue and worsen, among other phenomena. Because this issue is unlikely to resolve itself in the face of these dire climatic conditions, therefore the almond industry should utilize CRISPR-Cas9 engineering, since it can support and enhance the growth of California almond plants, on account of its potential to engineer agriculturally favorable phenotypes.

An ideal gene for such implementation in almond plants is the aforementioned SRO1 gene. As previously mentioned, it was linked to plant resilience under drought conditions, so the knockin of this gene has the potential to increase the fitness of the almond plant to the drier and more drought-prone conditions of California. For example, if the activity of the SRO1 gene promotes stomatal closure (or some other water-conserving mechanism) in *Prunus dulcis* as was observed in *Zea mays*, the almond plant would be able to store more water for a longer period of

time and thus consume less water overall. In drought-plagued growing seasons, this would be an obvious benefit to farmers, as the adverse rainfall conditions would not significantly interfere with the growth of their almonds. Furthermore, the reduced almond water demand would mitigate a major water consumption component of the overall state water demand, allowing water supplies to be conserved or diverted to other uses. Thus, less strain would be placed on water reservoirs, aquifers, and lake dams—aiding in long-term water security in California. Overall, the knockin of these genes via CRISPR-Cas9 technology would enable almonds and almond products to continue to sustainably support the California economy in the future with minimized water expenses.

Conclusion

CRISPR-Cas9 technology has and continues to foster innovation and breakthroughs in many different areas. In particular, its implementation in *Prunus dulcis* to introduce some of the aforementioned genes of interest has the potential to create hardier, more fortified, and more robust almond plants. Indeed, these modified plants are likely to bring great value to several human industries: from almond oil and energy production all the way to a significant portion of the economy of the state of California.

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Properties of Triangle Conics By Nguyen Vu Khanh Nguyen

Abstract/Summary

There are several papers published that contain a considerable amount of information in this triangle conic problem .Ruslan Skuratovskii's (Triangle conics and cubics) paper [1] introduce a significant number of new theorems and corollaries . Most of the newly-defined conics in this paper were based on well-known conics such as Jerabek hyperbola and Yff hyperbola .The content of the paper showed what they have found without proofs so in this paper I will prove some theorems of his paper to make it more explicit and clearer. I also introduced some new properties that I found .

Introduction

The number of research in triangles in Euclidean space has decreased in the past few centuries .One current interest area is conics related with triangles and some properties still remain unknown . My study is a summary of what people have already done in this field and it also explores properties in conics associated with triangles. In this paper , some classical geometry theorems appear along with properties that I've found .It also includes my proof of one Ruslan Skuratovskii's conic by using trilinear coordinates and proving my properties by using the classical geometry theorem.

Definition

Before reading the other part, point definition is a foremost thing .The list below contains all points and its definition that appeared in the research.

Point in triangle ABC:

+ E: Nine-point center : The midpoint between triangle's orthocenter and circumcenter. It also lies on the Euler lines which is a line passed through the triangle's centroid ,orthocenter and circumcenter. It is the center of the nine-point circle that passes through nine points of the triangle: the midpoints of the three edges, the feet of the three altitudes, and the points halfway between the orthocenter and each of the three vertices
+ de Longchamp points :the reflection of the orthocenter of the triangle about the circumcenter
+ Be: Bevan point : The center of the circle that pass through the centers of the three excircles of the triangle
+ Mi: Mittenpunkt point : The intersection of three lines that pass through the triangle's excenters and corresponding edge midpoints. In trilinear coordinate ,the Mittenpukt point is Mi : $\cot\frac{A}{2}$: $\cot\frac{B}{2}$: $\cot\frac{C}{2}$
+ Sy: Lemoine point :The intersection of the three symmedians (medians reflected at the associated angle bisectors) . In trilinear coordinate ,the Lemoine point is
  Sy: sin A : sinB :sin C

+ Isogonal conjugate of a point is constructed by reflecting the lines PA, PB, and PC about the angle bisectors of A, B, and C respectively. In trilinear coordinate ,the isogonal conjugate of a point x:y:z is x^{-1}:y^{-1}:z^{-1}.

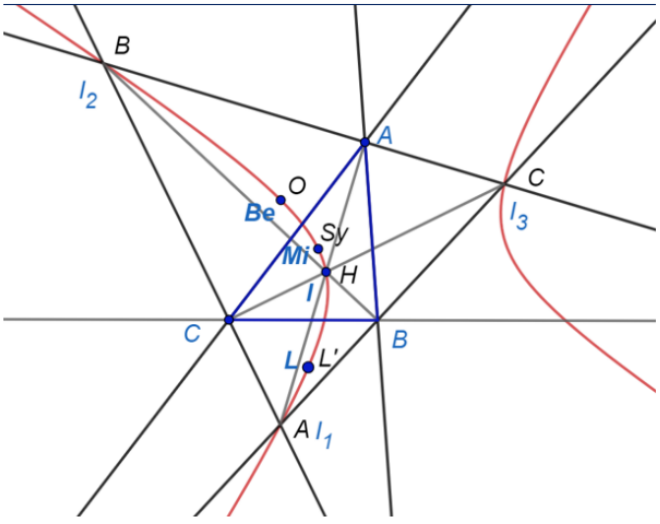
Conic Definition

+Jerabek hyperbola : circumconic passing through the vertices of triangle ,circumcenter , Lemoine point , orthocenter, it is a rectangular hyperbola and has center on the nine-point circle

Theorem

There are several papers published that contain a considerable amount of information in this triangle conic problem .Ruslan Skuratovskii's (Triangle conics and cubics)paper [1] introduce a significant number of new theorems and corollaries . In this part, I will use an advanced method called Trilinear coordinates to prove his theorems. Because Trilinear coordinates is more efficient than Cartesian coordinates in expressing linear function and proving two coincidence points. In his theorem below , he created a new hyperbola by using the well-known Jerabek hyperbola on the excentral triangle. In other words, Ruslan Skuratovskii's conic [1]is basically Jerabek hyperbola on the excentral triangle instead of the base triangle, and it passes through some specific points in the base triangle.

It passed through some points of the excentral triangle which is also another point of the base triangle.Some correspondences between points might be proved by using classical geometry . However , In this section I prove the correspondence between two points in triangle ABC and excentral triangle $I_1I_2I_3$



Ruslan Skuratovskii's conic [1] is a conic that passes through excenters, Bevan point, incenter, Mittenpunkt, de longchamps point. Its center lie on the circumcircle

+ Proof point I in triangle ABC is point H in triangle $I_1I_2I_3$

We have AI_1 is a bisector of BAC and AC is an external bisector of BAC

$\Rightarrow I_3$A $\perp$ AI_1 $\Leftrightarrow$ $I_2I_3 \perp I_1$I (because A , I , I_1 are collinear)

Similarly , I_2I $\perp I_1I_3$, I_3I $\perp I_1I_2$

$\Leftrightarrow$ I is an orthocenter in triangle $I_1I_2I_3$

$\Leftrightarrow$ I $\equiv$ H

We have the trilinear coordinate of point A, B ,C is

A : 1 : 0 : 0

B : 0 : 1 : 0

C : 0 : 0 : 1

We have I_1I_2 ,I_2I_3 , I_1I_3 equation in trilinear coordinate is

(I_1I_2) : x+y = 0;

(I_2I_3) : y+z = 0;

(I_1I_3) : z+x = 0;

(because trilinear of I_1 ,I_2 and I_3 is I_1 : -1 : 1 : 1 : 1 : -1 : I_3 : 1 : 1 : -1

+Proof Point Mi in triangle ABC is point Sy in triangle $I_1I_2I_3$.

We have coordinate of Mi in triangle ABC in trilinear coordinate : cot$\frac{A}{2}$: cot$\frac{B}{2}$: cot$\frac{C}{2}$

We have coordinate of Sy in triangle $I_1I_2I_3$ in trilinear coordinate : sinI_1 : sinI_2 : sinI_3 and we also have $\angle I_3I_1I_2 = \angle$BA$I_3$ (because I_2ABI_1 is a cyclic quadrilateral)

$\Rightarrow$ sinI_1 =sin(BAI_3) = sin ($\frac{\pi}{2}$- $\frac{A}{2}$) = cos $\frac{A}{2}$ so Sy : sinI_1 : sinI_2 : sinI_3 is equivalent to Sy : cos $\frac{A}{2}$: cos $\frac{B}{2}$: cos $\frac{C}{2}$

Then we have to calculate the coordinate of Mi in triangle $I_1I_2I_3$

$\Leftrightarrow$ Calculating the ratio of distances from Mi to I_1I_2, I_2I_3 and I_1I_3

The distances from Mi : cot$\frac{A}{2}$: cot$\frac{B}{2}$: cot$\frac{C}{2}$ to (BC) : y+z = 0

$$d_{(Mi\,,\,I_2I_3\,)} = \frac{0.cot\frac{A}{2}+1.cot\frac{B}{2}+1.cot\frac{C}{2}}{\sqrt{1^2+1^2+0^2-2.1.1cosA-2.1.0.cosB-2.0.1cosC}}$$

$d_{(Mi\,,\,I_2I_3\,)} = \frac{cot\frac{B}{2}+cot\frac{C}{2}}{\sqrt{2-2cosA}} = \frac{cot\frac{B}{2}+cot\frac{C}{2}}{2sin\frac{A}{2}}$ (because 1- cosA = cos0 − cosA = -2sin$\frac{-A}{2}$sin$\frac{A}{2}$ = 2si $n^2\frac{A}{2}$)

We have $cot\frac{B}{2} + cot\frac{C}{2} = \frac{cos\frac{B}{2}}{sin\frac{B}{2}} + \frac{cos\frac{C}{2}}{sin\frac{C}{2}} = \frac{cos\frac{B}{2}.sin\frac{C}{2}+cos\frac{C}{2}.sin\frac{B}{2}}{sin\frac{B}{2}.sin\frac{C}{2}}$ $\Rightarrow \frac{cot\frac{B}{2}+cot\frac{C}{2}}{2sin\frac{A}{2}} =$

$\frac{cos\frac{B}{2}.sin\frac{C}{2}+cos\frac{C}{2}.sin\frac{B}{2}}{2sin\frac{A}{2}.sin\frac{B}{2}.sin\frac{C}{2}} = \frac{sin\,(\frac{B}{2}+\frac{C}{2})}{2sin\frac{A}{2}.sin\frac{B}{2}.sin\frac{C}{2}}$

$= \frac{cos\frac{A}{2}}{2sin\frac{A}{2}.sin\frac{B}{2}.sin\frac{C}{2}}$ (because $\angle\frac{A}{2} + \angle\frac{B}{2} + \angle\frac{C}{2} = 90$)

Similarly

$d_{(Mi\,,\,I_1I_3\,)} = \frac{cos\frac{B}{2}}{2sin\frac{A}{2}.sin\frac{B}{2}.sin\frac{C}{2}}$,$d_{(Mi\,,\,I_2I_3\,)} = \frac{cos\frac{C}{2}}{2sin\frac{A}{2}.sin\frac{B}{2}.sin\frac{C}{2}}$

coordinate of Mi in triangle $I_1I_2I_3$: $d_{(Mi\,,\,I_2I_3\,)}$:$d_{(Mi\,,\,I_1I_3\,)}$: $d_{(Mi\,,\,I_2I_3\,)}$ =

$\frac{cos\frac{A}{2}}{2sin\frac{A}{2}.sin\frac{B}{2}.sin\frac{C}{2}} : \frac{cos\frac{B}{2}}{2sin\frac{A}{2}.sin\frac{B}{2}.sin\frac{C}{2}} : \frac{cos\frac{C}{2}}{2sin\frac{A}{2}.sin\frac{B}{2}.sin\frac{C}{2}}$

= cos $\frac{A}{2}$: cos $\frac{B}{2}$: cos $\frac{C}{2}$ = Sy

⇒ Mi in triangle ABC is point Sy in triangle $I_1I_2I_3$

+ Proof Point O in triangle ABC is point E in triangle $I_1I_2I_3$

  Because point E in triangle $I_1I_2I_3$ is the center of the nine-point circle and the nine-point circle pass through the foot A ,B ,C of each attitude I_1I , I_2I , I_3I

  ⇒ the nine-point circle of triangle $I_1I_2I_3$ is also the circumcircle of triangle ABC

  ⇒ O ≡ E .

  The center of the Jerabek hyperbola of triangle $I_1I_2I_3$ lie on the nine-point circle

  ⇒ Ruslan Skuratovskii's conic has the center lie on the circumcircle of triangle ABC

+ Proof Point Be in triangle ABC is point O in triangle $I_1I_2I_3$

Because in triangle ABC Be is the center of a circle which passes through three excentral of triangle ABC . That means Be is the center of the circumcircle of $I_1I_2I_3$

Properties

When I was exploding in the conic section I found some properties that I think are interesting . All properties below are proved by using classical geometry technique

Property 1 :

Given triangle ABC, D, E lie on the ray AB AC respectively such that BD = BC = CE. F, M lie on the ray BC BA respectively such that AC = CF = AM. N, P lie on the ray CA , BC respectively such that AB = AN = BP. Then there is a conic that passes through six points D, E, F, M, N and P.

Proof : There are several measures to prove this property by using geometric algebra such as : Cartesian coordinate, Trilinear coordinate ….. . However , I used Carnot's theorem to prove it because it is much faster than using geometric algebra.

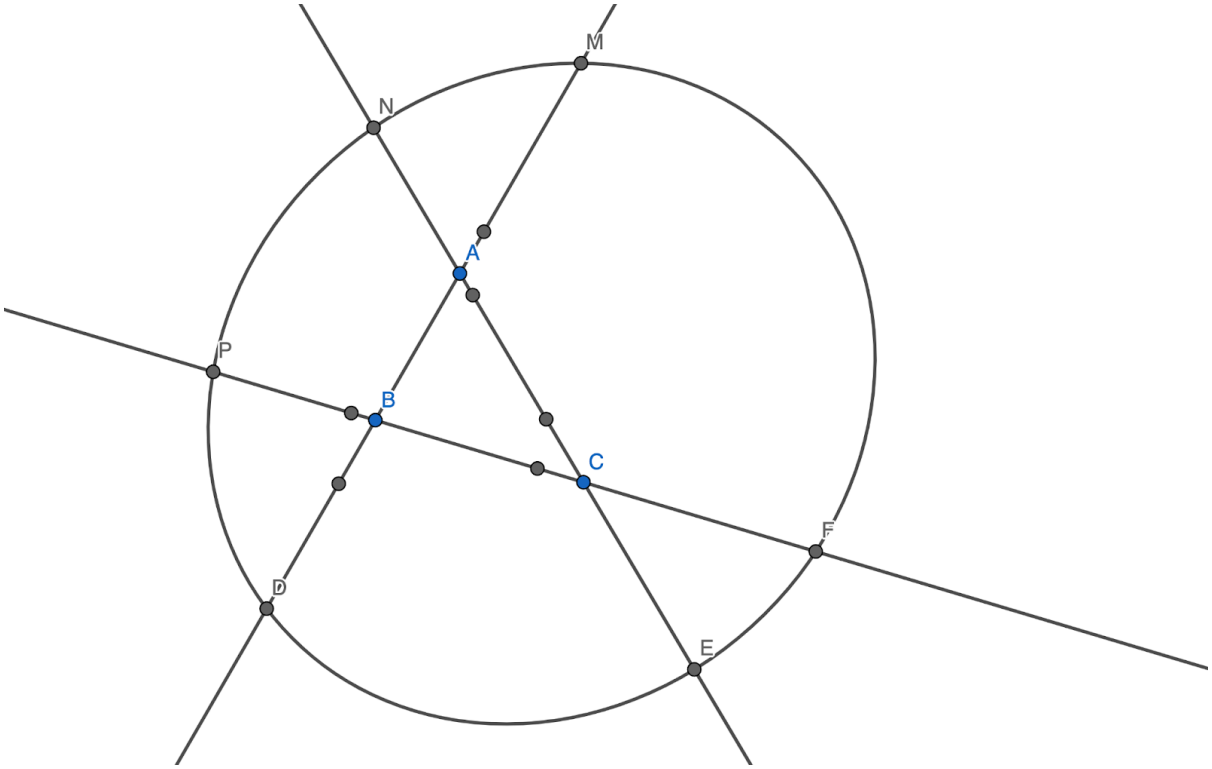


Figure 2

AM = AC = AF = b,
BD = BC = CE = a ,
AN = AB = BP = c,
Carnot's theorem proof :
https://www.cut-the-knot.org/triangle/CarnotForConics.shtml [2]

Because Carnot's theorem was proved by using the power of a point theorem when 6 points lie in 3 segments AB BC CA .In this case we will use the converse of the power of a point theorem.Thus, It is still correct if 6 points lie outside of 3 segments AB BC CA but still lie on line AB BC CA

Back to the property :

We have to prove D ,E ,F ,M ,N ,P lie on a conic .That is equivalent to prove :

$\Leftrightarrow \frac{AM}{BM} \cdot \frac{AD}{BD} \cdot \frac{BP}{CP} \cdot \frac{BF}{CF} \cdot \frac{CE}{AE} \cdot \frac{CN}{AN} = 1$

$\Leftrightarrow \frac{b}{b+c} \cdot \frac{c+a}{a} \cdot \frac{c}{a+c} \cdot \frac{a+b}{b} \cdot \frac{a}{a+b} \cdot \frac{b+c}{c} = 1$

This is obvious $\Rightarrow$ q.e.d

Property 2

Using figure 2 and then we connect some points to create segments and intersect .We have a new property (see figure 3)

Considered J is the intersection of MC and AF ,

I is the intersection of DC and BE,

K is the intersection of NB and AP,

Then there is a conic that passes through A ,J ,C , I ,B ,K and AI , BJ ,CK concur at O , which is the midpoint of each line

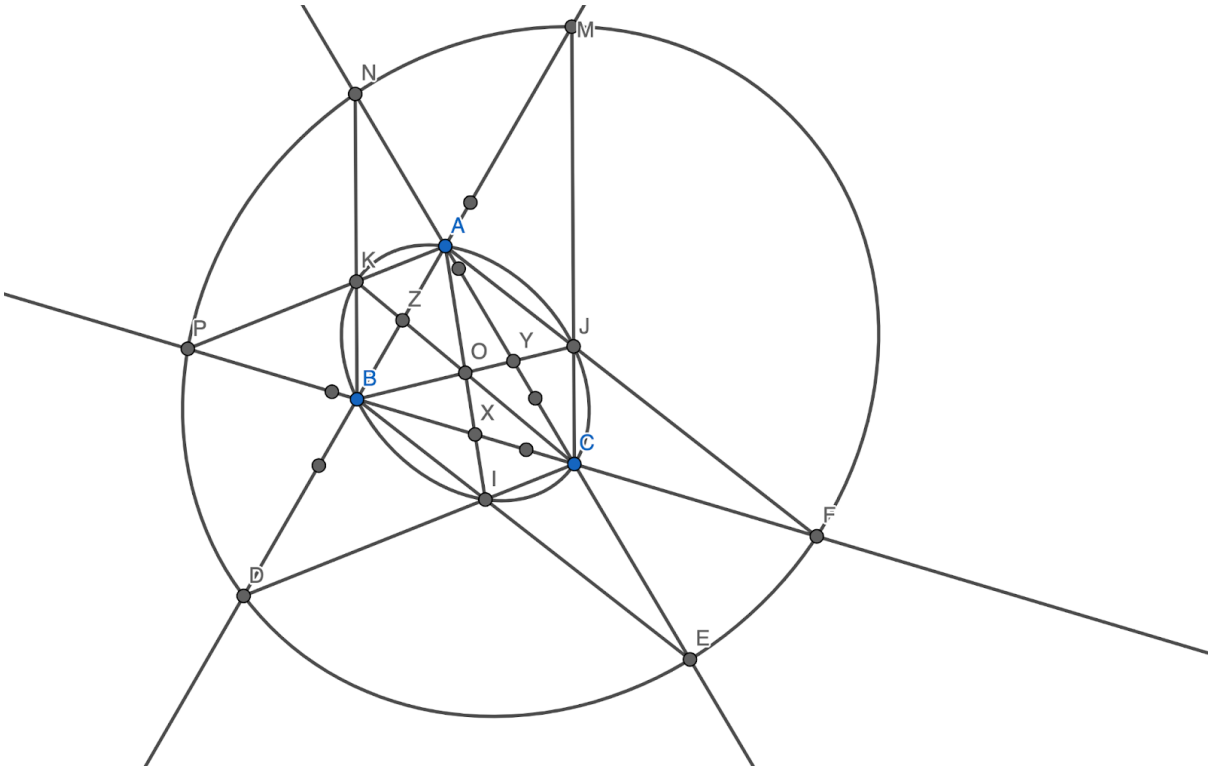


Figure 3

Proof : In this property I will use Pascal theorem and Menelaus theorem to calculate the ratio of some segments

In triangle ABE ,we have points C,I,D are collinear

$\Leftrightarrow \frac{EC}{CA}.\frac{AD}{BD}.\frac{BI}{IE} = 1$

$\Leftrightarrow \frac{a}{b}.\frac{a+c}{a}.\frac{BI}{IE} = 1$

$\Leftrightarrow \frac{BI}{IE} = \frac{b}{a+c}$

In triangle BCE , we have points I, X , A are collinear

$\Leftrightarrow \frac{BI}{IE}.\frac{EA}{CA}.\frac{CX}{BX} = 1$

$\Leftrightarrow \frac{b}{a+c}.\frac{a+b}{b}.\frac{CX}{BX} = 1$

$\Leftrightarrow \frac{BX}{CX} = \frac{a+b}{c+a}$

Similarly , $\frac{CY}{AY} = \frac{b+c}{a+b}$, $\frac{AZ}{BZ} = \frac{c+a}{b+c}$. Then it is obvious that AX , BY , CZ concur at O (Ceva's theorem)

Now we're going to prove that O is the midpoint of AI

We have $\frac{CY}{AY} = \frac{b+c}{a+b}$ and CY + AY = b

$\Rightarrow$ AY = $\frac{b(a+b)}{(a+b)+(b+c)}$,YC = $\frac{b(b+c)}{(a+b)+(b+c)}$;

$\Rightarrow \frac{AY}{YE} = \frac{AY}{YC + CE} = \frac{b}{a+b+c}$,

- In triangle AEI , we have points B,O,Y are collinear

$\Leftrightarrow \frac{AY}{YE}.\frac{EB}{BI}.\frac{IO}{OA} = 1$

$\Leftrightarrow \frac{b}{a+b+c}.\frac{a+b+c}{b}.\frac{IO}{OA} = 1$

$\Rightarrow$ OI = OA

Similarly OB = OJ , OC = OK .

$\Rightarrow$ AJIB , JBKC , CIKA are parallelogram.

$\Rightarrow$ AJCIBK form a parallel hexagon

$\Rightarrow$ There is a conic that passes through A ,J ,C , I ,B ,K . Q.e.d

Additional Result :

By using trilinear coordinates we can prove that O has the coordinate O : bc(b+c) : ca(c+a) : ab(a+b) ; O is the Spieker center in triangle ABC

Proof :

In this proof ,I combined classical geometry theorem and trilinear coordinate .We can calculate the ratio by using classical geometry theorem and then prove two points are concide by using trilinear coordinate

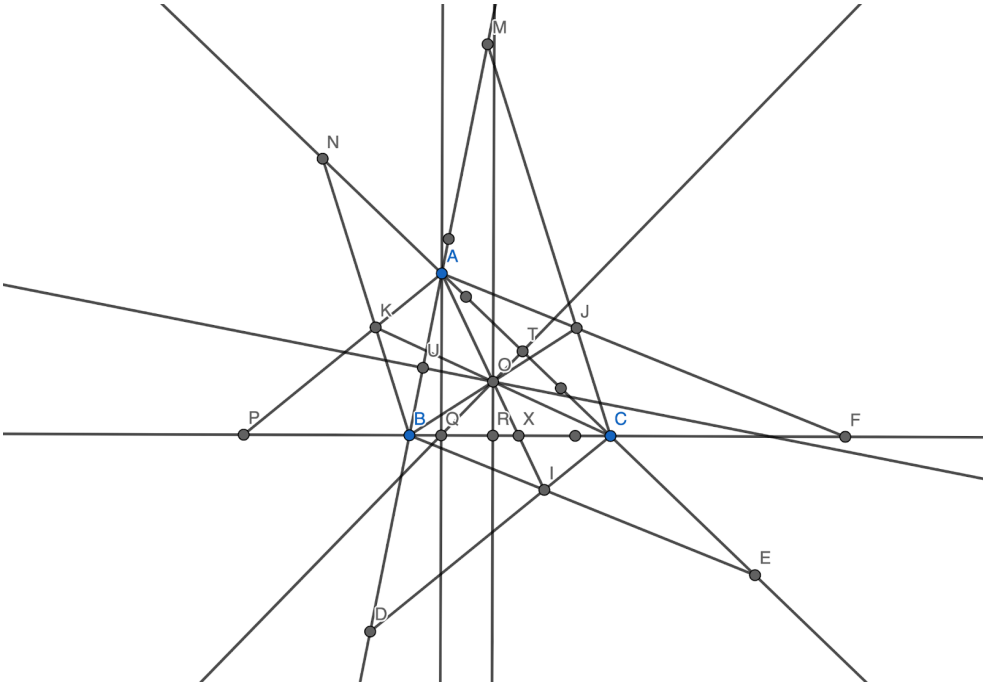


Figure 4

In triangle ABX ,we have Z, O, C are collinear

$\Leftrightarrow \frac{AZ}{ZB}.\frac{BC}{XC}.\frac{XO}{OA} = 1$

$\Leftrightarrow \frac{c+a}{b+c}.\frac{2a+b+c}{a+c}.\frac{XO}{OA} = 1$

$\Leftrightarrow \frac{XO}{OA} = \frac{b+c}{2a+b+c}$

$\Rightarrow \frac{XO}{XA} = \frac{b+c}{2(a+b+c)}$

From O and A We draw R, Q , OR ⊥ BC ,AQ ⊥ BC

$\Rightarrow \frac{OR}{AQ} = \frac{XO}{XA} = \frac{b+c}{2(a+b+c)}$

Considered S is the area of triangle ABC

$\Rightarrow$ AQ = $\frac{2S}{a}$, $\Rightarrow$ OR = $\frac{(b+c).S}{a(a+b+c)}$

Similarly we have OT , OU are the distances from O to AC , AB ,respectively.

$\Rightarrow$ OT = $\frac{(c+a).S}{b(a+b+c)}$, OU = $\frac{(a+b).S}{c(a+b+c)}$

$\Rightarrow$ The trilinear coordinate of O in triangle ABC O : OR : OT : OU

O : $\frac{(b+c).S}{a(a+b+c)}$: $\frac{(c+a).S}{b(a+b+c)}$: $\frac{(a+b).S}{c(a+b+c)}$

$\Leftrightarrow$ O : $\frac{b+c}{a}$: $\frac{c+a}{b}$: $\frac{a+b}{c}$ which is equivalent to

O : bc(b+c) : ca(c+a) : ab(a+b)

$\Rightarrow$ O is the Spieker center in triangle ABC

In conclusion , there is a conic that passes through vertices of triangle and the reflection of the vertices of triangle through Spieker point .

Methods:

In order to work on triangle conics , geometric algebra like coordinates seem to be one of the most popular ways to measure points . In addition , I also used some classical geometry theorem

Theorem

+ Pascal theorem states :if six arbitrary points are chosen on a conic and joined by line segments in any order to form a hexagon, then the three pairs of opposite sides of the hexagon meet at three points which lie on a straight line, called the Pascal line of the hexagon
+ Carnot theorem states : Given triangle ABC and D ,M lie on side AB , P, F lie on side BC , E,N lie on side AC . Then six points are located on a common conic
  $\Leftrightarrow \frac{AM}{BM} \cdot \frac{AD}{BD} \cdot \frac{BP}{CP} \cdot \frac{BF}{CF} \cdot \frac{CE}{AE} \cdot \frac{CN}{AN} = 1$
+ Menelaus theorem states : Given triangle ABC and D , E ,F lie on AB, BC, CA respectively .
  Then D,E,F are collinear $\Leftrightarrow \frac{AD}{BD} \cdot \frac{BE}{CE} \cdot \frac{CF}{AF} = 1$

+Ceva theorem states : Given triangle ABC and D , E ,F lie on AB, BC, CA respectively
  Then AE, BF , CD are concur $\Leftrightarrow \frac{AD}{BD} \cdot \frac{BE}{CE} \cdot \frac{CF}{AF} = 1$

+ I used the trilinear coordinates in order to prove two points are coincident . My method is : In triangle ABC and excentral triangle A'B'C' there are two points . Assume they are X and Y . X has the coordinate x:y:z in ABC . Y has the coordinate t:u:v in A'B'C' .I use trilinear coordinates to calculate a point X in the A'B'C' by calculating the ratio of the distances from X to B'C' ,A'C' ,A'B' . Considered that x':y'z' is the ratio of the distances from X to B'C' ,A'C' ,A'B' , then I prove that x':y':z' is equivalent to t:u:v .
+ I only use one formula to calculate the distance from a point to a line

The distance d from a point X: a' : b' : c' , in trilinear coordinates of actual distances, to a straight line Δ : lx + my + nz = 0 is

$$d_{(X,\Delta)} = \frac{la' + lb' + lc'}{\sqrt{l^2+m^2+n^2-2mncosA-2nlcosB-2lmcosC}}$$

Conclusion

In short , this paper represents the calculation of some proof by using trilinear coordinates. Additionally , I introduced the newly-defined conic and another definition of the Spieker point.

Works Cited

[1].Skuratovskii, Ruslan, and Veronika Strarodub. “Triangle Conics and Cubics.” arXiv.Org, 10 Jan. 2021, arxiv.org/abs/2009.01946.

[2]. Bogomolny, Alexander. Carnot’s Theorem for Conics, www.cut-theknot.org/triangle/CarnotForConics.shtml. Accessed 02/08/2022.

Analysis of Multiple Image Processing Algorithms for Detection of Melanoma
By Pranit Mathur

Abstract

This paper analyzes multiple machine learning algorithms such as “CNN for skin cancer detection” and “Triple Stratified KFold with TFRecords” for detecting skin cancer. Previous research revolving around skin cancer detection has different types of architectures like CNN’s Resnet, Resnet50, and EfficientNet tied to multiple different data sets. Data manipulation tactics makes the machine more accustomed to diagnosing skin cancer, usually with about a 60 to 65% accuracy. However, upon analyzing these 2 different machine learning algorithms, both ran at an accuracy of 82% and 91% respectively, much higher than the expected percentages present in literature.

Keywords

Deep learning, machine learning, skin cancer detection, algorithm, accuracy, efficiency, CNN, ANN

Introduction

Cancer is essentially when the cells inside your body grow in an uncontrollable way. There are over 200 types of cancer[1], but for the purposes of this paper the focus will be solely on skin cancer. Skin cancer is defined as the cancer affecting different cells on the epidermis and progressively moves inward, affecting other organs.[2] There are multiple different types of skin cancer including but not limited to Merkel cell cancer, Melanoma, and basal cell carcinoma. This paper will focus on a skin cancer detection algorithm revolving around melanoma. While Stage 0 and 1 have very low mortality rates once defined, stages 4 and 5 have very high mortality rates because the skin cancer has now affected multiple organs and distant parts of the skin.Countries such as India, Australia, New Zealand, and South Africa who have exposure to more ultraviolet(UV) light experience more cases of skin cancer.[3]

Some of the most serious symptoms of skin cancer are moles on the skin, redness or inflammation, and spots that become ragged or irregular. This requires effective diagnosing of the skin cancer cells as early as possible. Since the growth of computer vision and CAD studies many models being trained on Resnet50 and InceptionV3 have now allowed many more algorithms to produce more accurate and correct diagnoses of skin cancer. In fact, many of the detection algorithms for skin cancer have about a 60% accuracy whereas medical professionals only have a 23-46% accuracy[4], which is why improving upon these models is necessary. According to the National Health Institute, there is a large correlation between the level of UV light and the location and the development of melanoma, hence the increase of melanoma in Indian populations[5]. According to skincancer.org, more than 5.4 million cases of non-melanoma cancer were treated in just 2012 alone and over 2 to 4% of all cancers in Asians, showing that this affects almost 100,000,000 to 200,000,000 people globally[4].

A general problem that has been affecting the skin cancer research area is not being able to get a reliable algorithm to detect skin cancer over 60 to 65% accuracy due to the differing data sets, image shearing, and other variable factors[6].

Detection methods in skin cancer

Some of the methods that medical professionals use to detect skin cancer on their own is a visual examination (with a dermatoscope), a biopsy(part of the skin is tested at a lab to confirm whether or not skin cancer is present), and cancer screenings in addition to examining skin lesions, environmental factors, and age[4]. Despite this, a tool that a lot more medical professionals now rely on is machine learning: more specifically, models trained to diagnose skin cancer.

AI in Skin cancer

Machine learning has played an integral role in detecting and aiding medical professionals in their diagnosis of skin cancer. This specific type of problem is called a classification problem, which is when the supervised model has to try and assign a positive or negative value for each image of supposed “skin cancer”. The accuracy of both of these models were 82% and 91% accuracy respectively[5].

Efficiency of AI

The average algorithm usually runs at about 60 to 65% accuracy. Surprisingly, one of the algorithms ran at an astonishing 91% accuracy. It is important to note that this number is subjective because each dataset has its own requirements on image size, shearing(how the image is adjusted to correctly identify the type of skin cancer), etc[6].

Algorithm

A glimmer of hope reveals itself as there are key advancements in the areas of image processing, in addition to more datasets with annotated feedback from many doctors helping the algorithms to train more efficiently. CNN’s(convolutional neural networks) have been used extensively due to their effectiveness in pattern recognition[7]. In addition, the availability of these powerful machine learning models in a simple app format allows most of the world to use these softwares to accurately diagnose whether or not they have skin cancer[8]. One of the biggest problems with these sorts of algorithms is that these machine learning/deep learning algorithms need large vast data sets, otherwise suffering losses in their performance[9].

Review Aim

Analyzing two different melanoma detection algorithms step by step and understanding how they achieved the accuracy of over 80% on both of these models.

Algorithms

Triple Stratified KFold with TFRecords: This algorithm analyzes multiple resolutions of the same skin cancer image in the form of TFRecords. The algorithm will then distort the image to make it harder for the model to discern images from one another and perform 5 trials. The trial's accuracy is then averaged out and a final accuracy is found.

CNN for skin cancer detection: This algorithm focused on training, testing, and cross-validating a model to find both the best architecture(CNN's, DNN's, ANN's) to be used and the best model for the highest possible accuracy. The final accuracy is then displayed at the end.

Data Collection

Data was collected from ISIC (expansive collection of skin cancer images from around the world) as well as TFR Records which provided different resolutions for the same photographs used by the algorithm to either increase or decrease accuracy.

Data Analysis

In many machine learning models, a library is imported called matplotlib. This library allows for the models to print their results on graphs, which makes it easier for humans to analyze subsequently. These models often run in epochs (or trials) which is why multiple graphs for each algorithm have been displayed below.

Algorithm 1

Let's start with the first algorithm, which is on "CNN for skin cancer detection". This model's goal is to create a model that will determine if a skin cancer mole is benign or malignant. The first step is to import all of the essential libraries into the notebook(called a jupyter notebook) so that all of the machine learning code, which comes later, can be executed properly[10].

```
%matplotlib inline
import matplotlib.pyplot as plt
import numpy as np
import pandas as pd
import os
from glob import glob
import seaborn as sns
from PIL import Image
np.random.seed(11) # It's my lucky number
from sklearn.preprocessing import StandardScaler
from sklearn.model_selection import train_test_split, KFold, cross_val_score, GridSearchCV
from sklearn.metrics import accuracy_score
import itertools

import keras
from keras.utils.np_utils import to_categorical # used for converting labels to one-hot-encoding
from keras.models import Sequential, Model
from keras.layers import Dense, Dropout, Flatten, Conv2D, MaxPool2D
from keras import backend as K
from keras.layers.normalization import BatchNormalization
from keras.utils.np_utils import to_categorical # convert to one-hot-encoding
from keras.optimizers import Adam, RMSprop
from keras.preprocessing.image import ImageDataGenerator
from keras.callbacks import ReduceLROnPlateau
from keras.wrappers.scikit_learn import KerasClassifier
from keras.applications.resnet50 import ResNet50
from keras import backend as K
```

```
Using TensorFlow backend.
```

Figure 1: Imports of all libraries needed to run algorithms. These libraries include keras, matplotlib, sklearn, pandas, and seaborn.

Keras is a part of a neural network library called Tensorflow which specializes in building machine learning models(which is a program designed to use data to make predictions)[11]. Matplotlib is a library that makes animations and images in python and is used to visualize the outputs that the machine learning code gives us[12]. SkLearn is a machine learning library that implements a lot of algorithms that help with data analysis[13]. Pandas provides data structures and data analysis tools for visualization[14]. Seaborn is built on top of matplotlib and helps with graphs and charts of machine learning code[11].

Next, is the loading pictures and labeling them accordingly. First, the model separates the training data and the testing data into 2 separate folders[15]. Next the model will then combine the 2 data sets into one data set and shuffle both of the sets so the model has to "learn" how to identify the "skin cancer" and the "harmless moles".

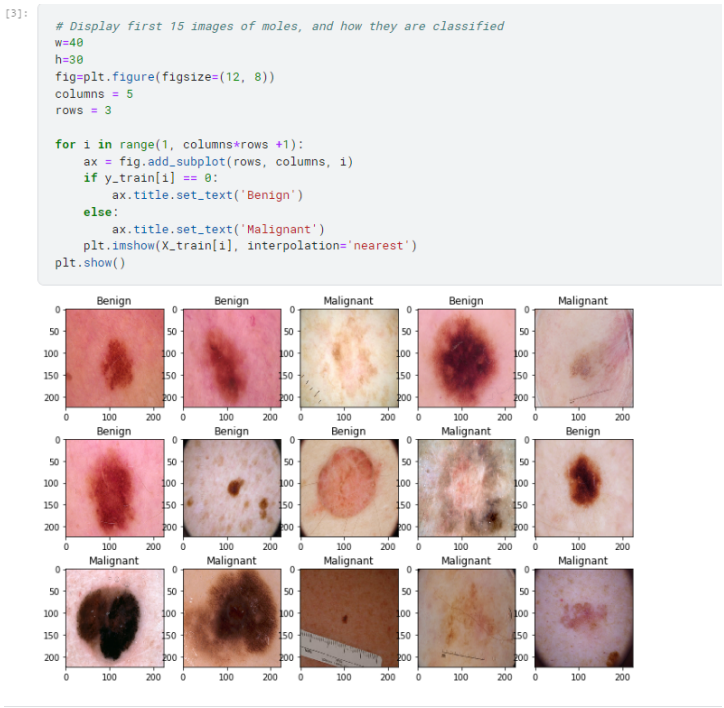


Figure 2: The code given loads the image in 3x5 format. Small subset of the images that are loaded, predetermined either benign or malignant.

The next steps are to categorize the data(meaning to encode or not let the machine decipher the labels)[16] and normalization, which attempts to eliminate biases/distortion by rescaling all of the values to a standard range[17].

The 5th step in this algorithm is to build the model using features such as dropout and downsampling to create convolutional layers. Downsampling is essentially trying to remove bias within the data set by taking a random equal sample out of a majority and comparing it to a random equal sample of a minority and comparing the two[18]. Dropout is taking certain neurons(called this because machine learning imitates how humans learn) and turning them off to

decrease the likelihood that only a few “active” neurons take over the entire network[19]. This ensures the idea that neurons will have an equal role in the CNN. Then, all of the features mentioned previously are then compressed down into an ANN(very similar to a CNN but uses nodes instead of neurons)[20]. It then sets up a learning annealer(or an optimal learning rate), sets up the history of the tests, and runs the model to see the results[21]. Here are the training data test results posted below.

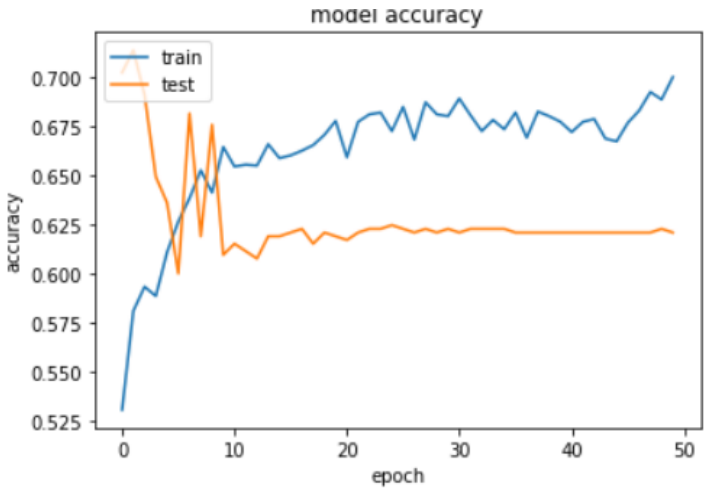


Figure 3: Model accuracy function of the train and test data of this model

On the x-axis are epochs, or trials that the model runs. The highest epoch accuracy is the one the model retains. Here, it is clear that usually as the epochs grow, the model adjusts and increases its accuracy.

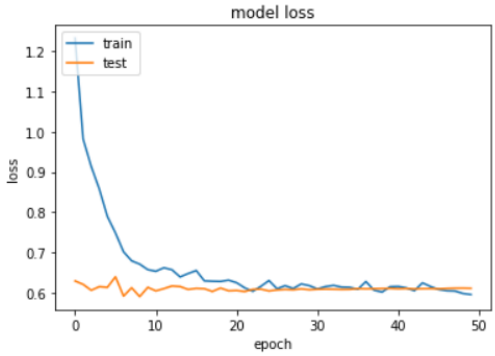


Figure 4: Model loss function of the train and test data of this model

The loss function is essentially how well a model fits a certain data set[22]. In this figure, in the beginning, the loss function is very high, indicating that the model does not fit the data well. However, as the epochs increase, the loss function decreases, indicating that the model is becoming increasingly more compatible with the data set.

In figure 3, the graph shows the model accuracy with both the training and test data, with blue showing train data and the orange showing test data. It is evident that the training accuracy is much higher than the testing accuracy, which is to be expected. The graph below shows the loss function for both the training and testing data, how varied the train loss is and how consistent the model loss is for the test data, showing the model is working very well.

The 6th step in the model is to cross validate the model, which essentially serves to take multiple subsets of the data, run the machine learning algorithm on each subset, take the average of all the subsets to have a much more accurate result of the true accuracy of the model[23]. In addition, it also serves to fine tune some of the parameters to make the overall algorithm much more efficient as a result.

```
_________________________________________________________________
Layer (type)                 Output Shape              Param #
=================================================================
conv2d_1 (Conv2D)            (None, 224, 224, 64)      1792
_________________________________________________________________
max_pooling2d_1 (MaxPooling2 (None, 112, 112, 64)      0
_________________________________________________________________
dropout_1 (Dropout)          (None, 112, 112, 64)      0
_________________________________________________________________
conv2d_2 (Conv2D)            (None, 112, 112, 64)      36928
_________________________________________________________________
max_pooling2d_2 (MaxPooling2 (None, 56, 56, 64)        0
_________________________________________________________________
dropout_2 (Dropout)          (None, 56, 56, 64)        0
_________________________________________________________________
flatten_1 (Flatten)          (None, 200704)            0
_________________________________________________________________
dense_1 (Dense)              (None, 128)               25690240
_________________________________________________________________
dense_2 (Dense)              (None, 2)                 258
=================================================================
Total params: 25,729,218
Trainable params: 25,729,218
Non-trainable params: 0
_________________________________________________________________
acc: 63.03%
```

Figure 5: 1st trial accuracy of cross validation model. The output that this particular fold has is a table.

On the left hand side are the different layers for the CNN's. Each layer has a specified shape and size with each layer handling a different aspect of the data set(called parameters). Most notably, the dense_1 layer is handling almost all of the parameters because there are many CNN's combined into a layer called an ANN. The final accuracy is then displayed at the bottom which is 63.03%

```
_________________________________________________________________
Layer (type)                 Output Shape              Param #
=================================================================
conv2d_1 (Conv2D)            (None, 224, 224, 64)      1792
_________________________________________________________________
max_pooling2d_1 (MaxPooling2 (None, 112, 112, 64)      0
_________________________________________________________________
dropout_1 (Dropout)          (None, 112, 112, 64)      0
_________________________________________________________________
conv2d_2 (Conv2D)            (None, 112, 112, 64)      36928
_________________________________________________________________
max_pooling2d_2 (MaxPooling2 (None, 56, 56, 64)        0
_________________________________________________________________
dropout_2 (Dropout)          (None, 56, 56, 64)        0
_________________________________________________________________
flatten_1 (Flatten)          (None, 200704)            0
_________________________________________________________________
dense_1 (Dense)              (None, 128)               25690240
_________________________________________________________________
dense_2 (Dense)              (None, 2)                 258
=================================================================
Total params: 25,729,218
Trainable params: 25,729,218
Non-trainable params: 0
_________________________________________________________________
acc: 78.73%
```

Figure 6: 2nd trial accuracy of cross validation model.

In figure 6, it is very clear that most of the items are identical to the figure above. However, one key difference is the accuracy this model gives, which is 78.73%, indicating that the model has improved.

```
_________________________________________________________________
Layer (type)                 Output Shape              Param #
=================================================================
conv2d_1 (Conv2D)            (None, 224, 224, 64)      1792
_________________________________________________________________
max_pooling2d_1 (MaxPooling2 (None, 112, 112, 64)      0
_________________________________________________________________
dropout_1 (Dropout)          (None, 112, 112, 64)      0
_________________________________________________________________
conv2d_2 (Conv2D)            (None, 112, 112, 64)      36928
_________________________________________________________________
max_pooling2d_2 (MaxPooling2 (None, 56, 56, 64)        0
_________________________________________________________________
dropout_2 (Dropout)          (None, 56, 56, 64)        0
_________________________________________________________________
flatten_1 (Flatten)          (None, 200704)            0
_________________________________________________________________
dense_1 (Dense)              (None, 128)               25690240
_________________________________________________________________
dense_2 (Dense)              (None, 2)                 258
=================================================================
Total params: 25,729,218
Trainable params: 25,729,218
Non-trainable params: 0
_________________________________________________________________
acc: 67.12%
```

Figure 7: 3rd trial accuracy of cross validation model.

In figure 7, much like figures 5 and 6, much of the information is the same. However, looking at the accuracy, it has dropped to about 67.12%, meaning that the model has incorrectly determined the best way to increase the accuracy.

Taking the average of all of these different accuracies yields an average of 69.62% across the entire model, which is confirmed by figure 8.

```
69.62% (+/- 6.65%)
```

Figure 8: Average accuracy of the 3 trials

The 7th step and 8th step is to actually test the model by adjusting the parameters and testing on different CNN's to increase the overall accuracy and performance of the model. After running 50 epochs(or tests), the final results have been displayed below.

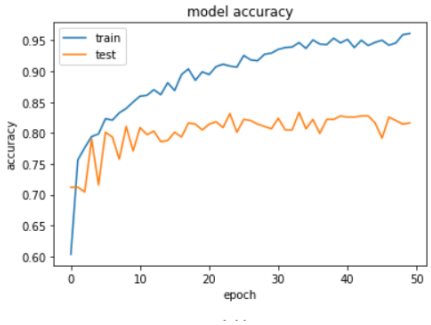


Figure 8: final model accuracy function of the train and test data

In figure 8, both the train data and the test data for each epoch is graphed above. As mentioned previously, the test data is the model trying to apply patterns and similarities of skin cancer to a completely new data set and is the accuracy that is recorded(note that the train accuracy is significantly higher than the test accuracy).

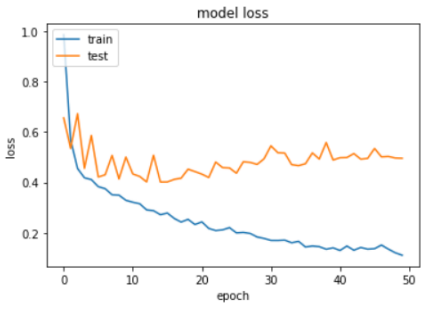


Figure 9: final model loss function of the train and test data

In figure 9, both the train and test data for each epoch is graphed above. As mentioned previously, the test data is the model trying to apply patterns and similarities of skin cancer to a completely new data set. However, in this figure, instead of accuracy, it is a loss function. Like

mentioned previously, the loss function shows how well a model fits the data(the lowest value is the recorded).

```
0.8212121212121212
Saved model to disk
```

Figure 10: Model's final accuracy in numerical value.

Algorithm 2

Now, let's move onto the second algorithm, which is called "Triple Stratified KFold with TFRecords". Similar to the previous algorithm, this algorithm imports similar softwares such as matplotlib, keras, and pandas to do tasks described above. Then, training and testing data were split up into 2 separate folders and showed some examples of labeled melanoma or benign cases.

The second step is to initialize the environment where the algorithm connects to either the TPU or the GPU of the computer.

The third step is actually when the algorithm begins to transform some of the training and testing images to make it more difficult for the algorithm to correctly identify the image.

Then the algorithm actually builds the model using multiple different architectures like ResNet50, ResNet, and CNN. In this particular algorithm, 6 layers called EfficientNets are used.

Then the algorithm actually runs with 5 repetitions called folds to determine the maximum accuracy. Throughout these folds, the algorithm will make slight changes to try and optimize the maximum accuracy possible[24].

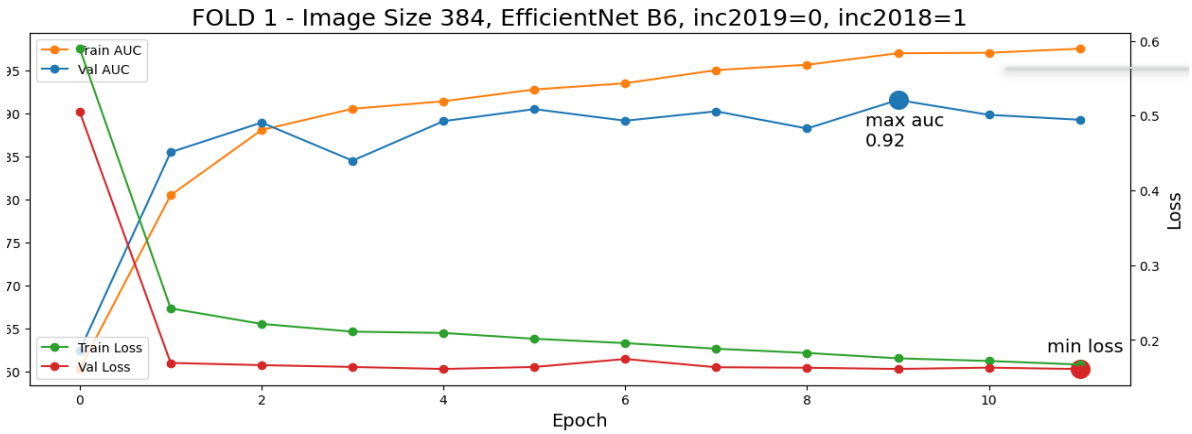


Figure 11: First iteration of the machine learning model with train and loss function

In figure 11, we see the train and test (labeled as Val) graphed above. As mentioned above, the maximum accuracy is the highest point graphed(Also called A.U.C. because it is also the maximum area under the curve). In this fold (or trial), the maximum accuracy was 0.92 or 92%.

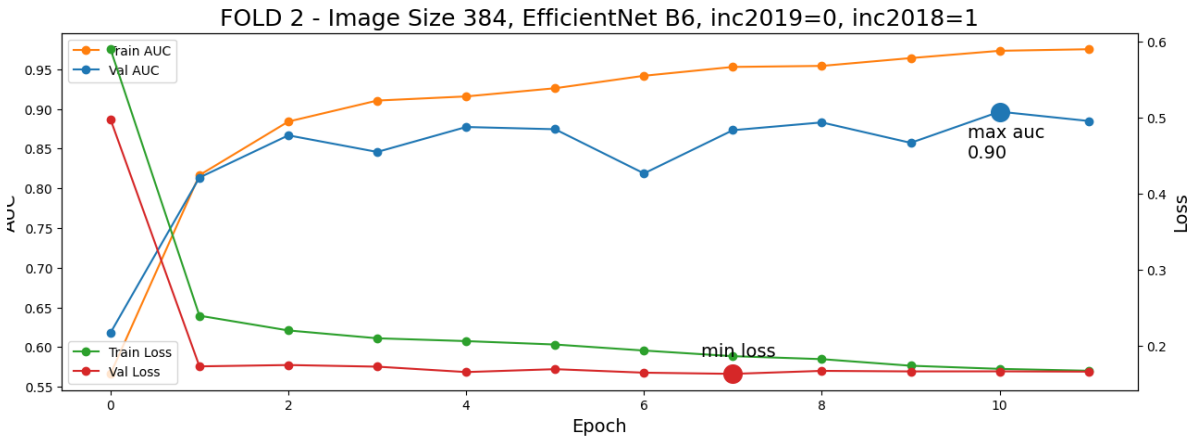


Figure 12: Second iteration of the machine learning model with train and loss function

In figure 12, we see the train and test(labeled as Val) graphed above. As mentioned above, the maximum accuracy is the highest point graphed(Also called A.U.C. because it is also the maximum area under the curve). In this fold (or trial), the maximum accuracy was 0.90 or 90%.

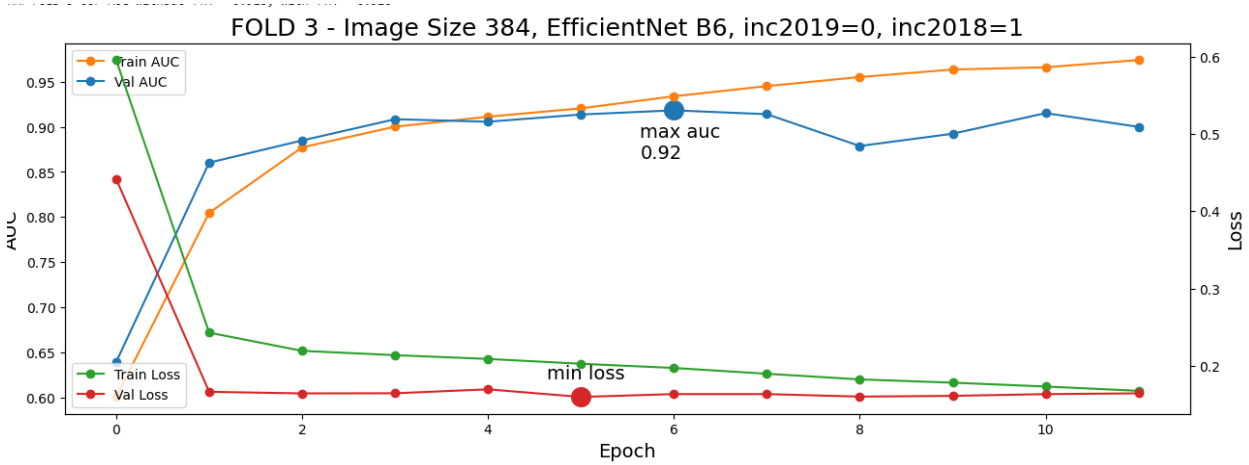


Figure 13: Third iteration of the machine learning model with train and loss function

In figure 13, we see the train and test(labeled as Val) graphed above. As mentioned above, the maximum accuracy is the highest point graphed(Also called A.U.C. because it is also the maximum area under the curve). In this fold (or trial), the maximum accuracy was 0.92 or 92%.

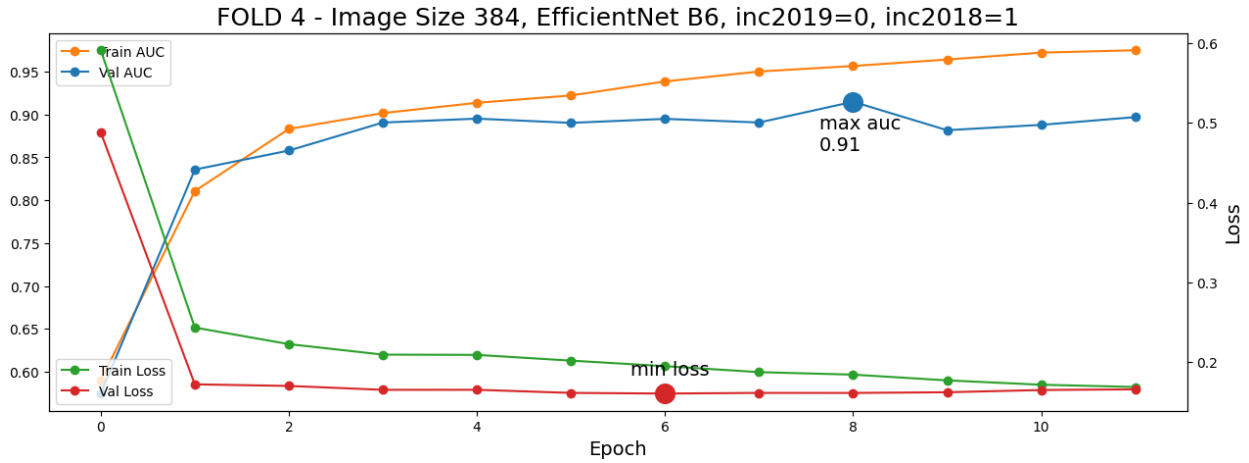


Figure 14: Fourth iteration of the machine learning model with train and loss function

In figure 14, we see the train and test (labeled as Val) graphed above. As mentioned above, the maximum accuracy is the highest point graphed (Also called A.U.C. because it is also the maximum area under the curve). In this fold (or trial), the maximum accuracy was 0.91 or 91%.

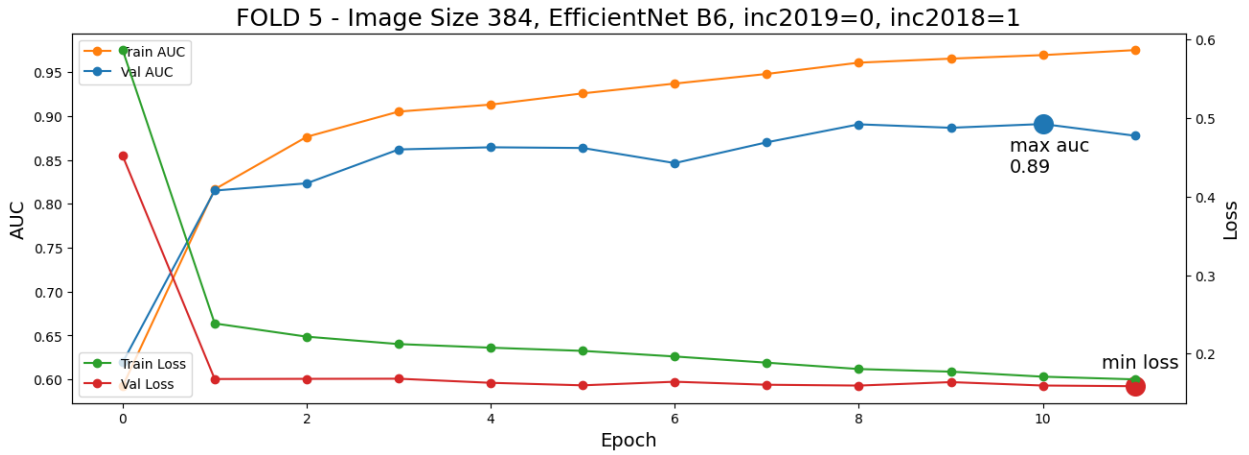


Figure 15: Fifth iteration of the machine learning model with train and loss function

In figure 15, we see the train and test (labeled as Val) graphed above. As mentioned above, the maximum accuracy is the highest point graphed (Also called A.U.C. because it is also the maximum area under the curve). In this fold (or trial), the maximum accuracy was 0.89 or 89%.

The final accuracy is all of the different iterations' accuracies averaged out. This particular algorithm averaged out to 91%.

Conclusion

In conclusion, this paper focused on how two skin cancer algorithms functioned. Both algorithms had a similar process of developing the algorithm with final accuracies of 82% and

91% respectively. With this knowledge in mind, the new algorithm combines many of the strengths (timing, optimizer, label-smoothening, etc.) to improve upon the accuracy of these detection algorithms.

Although both algorithms can consistently predict different types of skin cancer at above 80% accuracy, there are a few places where both algorithms can be improved. For one, the first algorithm ran fairly quickly, at about 1 hour. The model's final accuracy at 82% can be improved significantly if the values in the learning rate, epochs, validation_split, and a different type of CNN (such as ResNet or ResNet50) was used instead. For the second algorithm, although it performed at a much higher accuracy (around 91% but dont have the actual image to corroborate this statement), the run-time needs to be limited significantly as it takes about an entire day to run the code(limiting the number of epochs). In addition, adjusting some of the optimizer, label-smoothening, and learning-rate of this algorithm can also be tweaked to reduce the loss-function(hence increasing the overall accuracy). In order to tweak the values much more efficiently, a reduction in the number of trials(epochs) is required from 12 to 7[25].

Once improved, these machine learning models have the potential to become much more reliable in the diagnosis and aiding of medical professionals. Once the accuracy becomes above 95%, it is almost a guarantee(technically can't really have 100% accuracy with a machine learning model[26]) that both dermatologists and oncologists alike can use this algorithm to more accurately detect and diagnose skin cancer. This algorithm will be deployed in an app format so that doctors or users alike can scan a body part or an image and have it tell you whether or not it is skin cancer or not. In addition, it also helps with public health awareness. By informing patients and doctors alike about the importance of sunscreen, wearing sun-glasses, and practicing proper skin hygiene, skin cancer rates plummet significantly[27].

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Failures in AD Clinical Trials: How Will They Change the Future? By Aleeza Dhillon

Abstract

This paper investigates the reasons why clinical trials for treatments of Alzheimer's disease (AD) have failed and makes recommendations for improvement. The intricate AD pathophysiology, poor patient selection, inadequate dosage, and inappropriate trial design are a few of the factors contributing to clinical trials' low success rates. The research examines the use of imaging biomarkers, Aβ, tau proteins, and other biomarkers in patient selection and diagnosis. It also talks about the ε4 allele and APP gene mutations as genetic risk factors for AD. The article highlights the requirement for a greater understanding of the underlying mechanisms causing AD and the creation of specialized treatment procedures that address various parts of the illness.

Introduction

Alzheimer's disease (AD) is a progressive neurological condition marked by memory loss and cognitive deterioration. Biological indicators for AD include accumulating amyloid (Aβ) plaques and neurofibrillary tangles (NFTs) in the brain (DeTure, 2019). Despite substantial studies, clinical studies for potential AD therapies have routinely failed in recent years. We'll examine the factors that led to AD clinical trial failures and suggest potential improvements.

Multiple factors contribute to trial failures, including the complicated nature of AD pathogenesis, poor patient selection, insufficient dosage, and ineffective trial design (Yiannopoulou, 2019). The majority of current therapeutic trials use single-target strategies that do not address the complex pathology of AD. Therefore, clinical trials have had a low success rate (Cummings, 2020). An in-depth knowledge of AD pathogenesis and its heterogeneity is needed to improve the success of AD trials. This includes the discovery of biomarkers to improve patient selection, the creation of individualized therapy plans, and the addition of several therapeutic targets.

Identifying AD

Biomarkers have recently come to light as crucial tools for the identification and diagnosis of AD. The measurement of Aβ in the cerebrospinal fluid (CSF) is one of the most well-established biomarkers for AD (Nojima, 2022). According to studies, people with AD had reduced amounts of Aβ in their CSF. Additionally, it has been demonstrated that the ratio of Aβ42 to Aβ40 in the CSF is a good indicator of AD, with lower ratios indicating a higher chance of contracting the condition (Hansson, 2019). Aβ is an aggregation-prone and toxic polypeptide; the difference between Aβ42 and Aβ40 is two amino acid residues (Qiu, 2015). Another protein that is used as a biomarker is tau, a protein found mainly in neurons and is responsible for many healthy functions within the brain cells (Ellison, 2022). Measuring the amount of tau protein in the CSF is a crucial diagnostic for AD. The protein tau plays a crucial part of the stability of microtubules in neurons. NFTs develop in the brain as a result of hyperphosphorylation of tau

protein in AD. According to studies, people with AD had greater tau levels in their CSF, which may be a result of the buildup of NFTs in their brains (Fagan, 2010). Imaging biomarkers for AD have also been developed as a result of recent developments in neuroimaging. Amyloid PET imaging is one such biomarker, which makes use of radiotracers to show the buildup of Aβ plaques in the brain. Amyloid PET imaging can identify Aβ accumulation in AD patients and distinguish AD from other types of dementia (Suppiah, 2019). Structural MRI is another imaging biomarker for AD and can recognize changes in brain size in areas where AD disease is present.

The likelihood of AD can be influenced by hereditary factors. The ε4 allele is one of the most well-known genetic risk factors for Alzheimer's disease. An important indicator of AD is the accumulation of beta-amyloid protein in the brain, which is caused by the ε4 allele function in the transport and metabolism of lipids. A person is more likely to develop AD if they have one or two copies of the ε4 allele (Raulin, 2022). Another gene connected to Alzheimer's disease is the amyloid precursor protein (APP) gene, which codes for a protein implicated in the formation of beta-amyloid plaques (Chen, 2017). Mutations in the APP gene are responsible for both the overproduction of beta-amyloid protein and early-onset Alzheimer's disease.

History of Clinical Trials

Clinical trials have been overwhelmed by a high rate of failure, despite attempts to create effective treatments for AD. This highlights the complexity of the disease and the demand for a deeper comprehension of its underlying mechanisms. As a result, focusing on a single element of AD pathology might not be enough to have a significant therapeutic impact.

Another biological aspect that contributes to the failure of AD clinical trials is poor patient selection. While the degenerative changes in the brain may have already taken place decades before the onset of clinical symptoms, patients with mild to moderate AD disease were frequently enrolled in past clinical trials for the condition (Wenk, 2003). It is more difficult to appropriately assess the effectiveness of possible treatments in patients with late illness stages since they frequently have higher cognitive impairment. Determining the precise benefits of the trial is difficult since patients with numerous health disorders could not respond to treatment in the same manner as people without these conditions (Fogel, 2018). Additionally, it is challenging to design treatments that are efficient for all individuals due to the variability of AD, which has a variety of subtypes and underlying causes. Research demonstrates that those who have preclinical AD biomarkers are more likely to develop AD (Cummings, 2020). In order to stop or delay the advancement of the disease, it may be more effective to treat individuals when they are at an earlier stage of the condition.

Inadequate dosage of supposed therapies is another biological aspect that has contributed to the failure of clinical studies for AD. Numerous prior AD clinical trials employed doses that may not have been adequate to produce therapeutic results, according to studies. An anti- Aβ antibody clinical trial, for instance, used doses that were lower than those necessary to produce efficient Aβ clearance in preclinical models (Lemere, 2010).

In addition, given the complexity of AD pathophysiology, current trial designs might not be ideal. Traditional randomized controlled trial designs, which were frequently employed in earlier AD clinical studies, might not be the most effective way to assess AD therapies. For instance, RCTs frequently have predetermined study lengths that might not be sufficient to assess the long-term effects of AD therapies. Furthermore, RCTs frequently rely on goals related to cognition and functionality, which cannot fully reflect the molecular changes causing AD (DeTure, 2019).

Expedition 3: A Failure

The Expedition 3 experiment, a phase III clinical trial of solanezumab, a monoclonal antibody that targets brain amyloid plaques, is one instance of a particular AD clinical trial that has failed in recent years (Doody, 2014). The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) score change from baseline at 80 weeks was the trial's primary outcome, which included 2,129 patients with moderate AD dementia (Doody, 2014). The ADAS-Cog score difference between the solanezumab and placebo groups was not statistically significant (p=0.095), so the experiment did not achieve its primary aim. The Expedition 3 trial may have failed for a number of reasons (Doody, 2014). Solanezumab's failure to effectively target brain-amyloid plaques is one possibility that could apply, given that the treatment's impact size was less distinct than anticipated. Another reason is that the experiment may have been underpowered, meaning the sample size was not big enough to successfully determine the effectiveness of the drug. Additionally, because patients with moderate AD dementia may have had less severe -amyloid pathology than those with more advanced stages of the illness, the inclusion of these patients may have lessened the impact of the treatment. The Expedition 3 trial's findings are in line with other recent clinical trials of -amyloid-targeted treatments, which have likewise been unable to show any discernible cognitive advantages in patients with AD dementia (Honig, 2018).

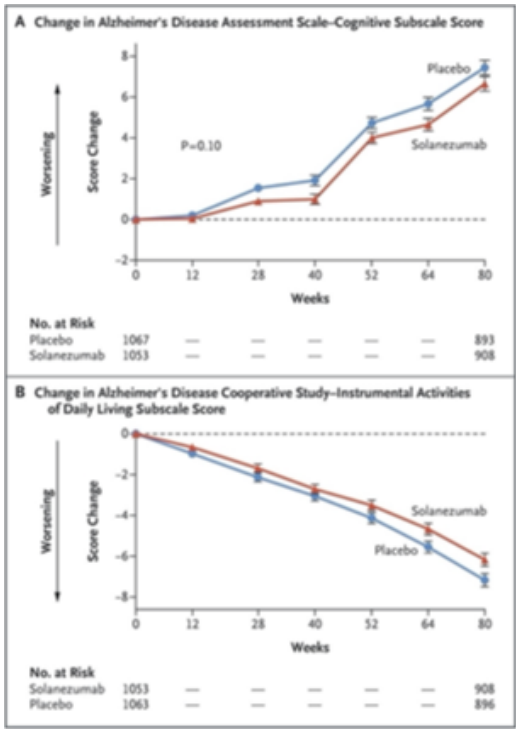

Figure 1. Panel A displays the findings of the primary outcome, which is the average change from baseline (represented by a dashed line) in the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale.

Higher scores indicate more significant cognitive impairment. Meanwhile, Panel B shows the outcomes of the secondary functional outcome of the average change from baseline (represented by a dashed line) in the instrumental subscale of the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory. Lower scores indicate a greater functional loss. There was no notable discrepancy observed between the groups at week 80 regarding the alteration in their score compared to their baseline (Honig, 2018).

Future Implications

Future clinical studies of -amyloid-targeted treatments, like the Expedition 3 study, could be enhanced in a number of ways. In order to ensure that the patient group has a more uniform amount of -amyloid pathology, the inclusion criteria could first be improved (Srivastava, 2021). Since these individuals may have had less severe -amyloid pathology than patients with more advanced stages of the disease, adding patients with moderate AD dementia in Expedition 3 may have lessened the treatment's impact. Future studies might select patients with higher levels of amyloid pathology using biomarkers, which can improve the chance of therapeutic benefit.

Second, the trial's duration could be lengthened for patient follow-up over a longer period of time. The experiment in Expedition 3 lasted 80 weeks, which might not have been long enough to notice a therapeutic impact (Cummings, 2020). Longer treatment periods may be considered in subsequent trials in order to delay or stop the disease's progression.

Thirdly, it may be possible to investigate combination therapy that takes aim at various pathways involved in the etiology of AD. Medicines that target other components of the disease, like neuroinflammation or tau pathology, may be more effective when combined with medicines that target -amyloid. Overall, the Expedition 3 trial's failure serves as a reminder of the difficulties in creating AD treatments and the pressing need for more investigation into the disease's fundamental causes. Future studies might examine the use of combination medicines to boost healing effectiveness.

Aducanumab: The Future

Aducanumab, another monoclonal antibody that targets -amyloid plaques, was tested in the ENGAGE and EMERGE trials (Cambridge, 2019). It has been approved by the Food and Drug Administration (FDA) as an acceptable treatment for AD. The medication specifically targets beta-amyloid protein, which is thought to cause plaques in the brain and contribute to the onset of Alzheimer's disease (Beshir, 2022). In clinical studies, the anti-beta-amyloid drug aducanumab was found to halt cognitive loss in people with early-stage Alzheimer's disease. It has been demonstrated to decrease the brain's beta-amyloid levels (Beshir, 2022).

Table 1. Met the primary and secondary objectives. Positive result on tertiary endpoint-87% less decline v. Placebo.

	Study 302 Final Data		
	Week 78 Placebo decline (N=548)	Week 78 Difference vs. placebo (%) p-value	
		Low Dose (N=543)	High Dose (N=547)
CDR-SB	n=288 1.74	n=290 **-0.26 (-15%)** 0.0901	n=299 **-0.39 (-22%)** 0.0120
MMSE	n=288 -3.3	n=293 **-0.1 (3%)** 0.7578	n=299 **0.6 (-18%)** 0.0493
ADAS-Cog 13	n=287 5.162	n=289 **-0.701 (-14%)** 0.1962	n=293 **-1.400 (-27%)** 0.0097
ADCS-ADL-MCI	n=283 -4.3	n=286 **0.7 (-16%)** 0.1515	n=295 **1.7 (-40%)** 0.0006

Low does for primary endpoint and two secondary endpoints display numerically favorable results (FDA, 2019).

However, due to inconsistent findings from clinical trials, Aducanumab's effectiveness has been a subject of discussion, and further study is required to comprehend its long-term consequences and advantages properly (Vaz, 2022). In addition to being costly and requiring monthly infusions, the medication might be highly burdensome for both patients and the healthcare system. Therefore, researchers must continue to change clinical trial designs in order to find more effective treatments for AD. In the future, clinical trials should reflect the effective strategies observed in previous trials but change those aspects that have been proven to lead to a growing failure rate.

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How Have Marketing and Advertising Strategies Influenced Buyers and Contributed to the Prevalence of the Pink Tax? By Kashish Arora

Abstract

This research paper explores the social issue of gender inequality, tracing its roots back to the Bronze Age and highlighting its amplified prevalence in the 21st century. Specifically, it focuses on the manifestation of gender inequality through the concept of the "Pink Tax," which refers to the gender-based price disparities that result in women paying more for similar products or services. The paper investigates the marketing strategies employed by firms to target women and assesses the general awareness of the Pink Tax among the public. The study adopts an exploratory approach, utilizing surveys and case studies to gather data and insights. The results indicate a concerning lack of awareness regarding the Pink Tax, with only a small percentage of respondents demonstrating a thorough understanding of the issue. Additionally, the study reveals how marketing techniques, such as gendered packaging and product design, influence women's susceptibility to the Pink Tax. The findings underscore the need for increased awareness, policy interventions, and further research to address and mitigate gender-based pricing discrimination.

Keywords: Pink Tax, Gender Inequality, Gendered Marketing, Consumer Perceptions, Colour Psychology

Introduction

The social issue of gender inequality may have its seeds in the Bronze Age more than 2,500 years ago, where men would be buried with more riches and were even the first ones to get food when it was low in supply. (The 2,500-year-old Roots of Gender Inequality - the Boston Globe, 2017) Even in the 21st century, this issue plagues our world. Gender inequality is defined as discrimination on the basis of sex or gender causing one sex or gender to be routinely privileged or prioritized over another. (Gender Discrimination Causes Inequality Between Girls and Boys Around the World, n.d.) Females are considered to be the inferior gender as opposed to males. The issue manifests itself in various ways, commonly such as unequal pay, limited access to education and healthcare, gender-based violence, and underrepresentation of women in political and economic leadership positions.

In 2009, Harvard Business Review found that women drive between 70 and 80% of all consumer purchasing. Women were considered to be dainty, graceful, petite and fragile and hence multiple firms birthed the marketing strategy termed as “Pink it and Shrink it”. (Contrera, 2016) This strategy involves taking an everyday product, manufacturing it in pink, and making it smaller in size for women to use. (Mertes, 2011)

As a matter of fact, women are even made to pay more in taxes. This brings us to the concept of the pink tax. The pink tax is a gender based price disparity which drives women to pay an extra amount as consumers for products and services that are similar or equal in merit to corresponding men’s products. (What Is the ‘Pink Tax’ and How Does It Hinder Women?, n.d.)

For example, the BIC For Her pens gained a lot of attention worldwide. What differentiated these pens from the regular pens was that the design was more sleek. This design was thought to be of better fit to women due to their hands being smaller in size and thinner. The use of sterooeotypical women colours such as pink and purple was also a strategy to attract more women into buying the product. (Here Are the Bic Pens for Women That Everyone Is Laughing At, n.d.) Even the name of the product “For Her” prompted consumers to believe that these pens were the absolute best fit for any women looking for writing material.

The pink tax is most prevalent in the Beauty and Wellness industry. Not to mention, advertising, marketing, and pricing strategies uptaken by producers only fuels the susceptibility of female consumers to the Pink Tax. Firms make use of gendered marketing to target women by using images, language, and colours that appeal to feminine stereotypes. This includes the heavy use of the colour pink, and images such as flowers and hearts. Furthermore, firms may differentiate products for men and women by changing the packaging and product design while their features remain near homogeneous. Women’s products would be marketed as higher quality, eg. a razor being "gentler" or "softer," which allows firms to charge a premium for them. A very common example is womens razors costing 50 cents (13%) more than mens razors. However, the features and functionality of the product is identical. The only aspect that differs is the colour of the razors, and how they are marked as “gentle” and “non-harmful” to the skin. (Pink Tax Study: Women Pay 13% More for Gender-marketed Products, 2022) Additionally, firms also make use of such strategies as they perceive women as the gender who would pay a premium pricing as they are more concerned about their physical appearance as compared to men. By using these marketing techniques, firms can charge more for women's products and perpetuate the pink tax.

Not a lot of literature exists about how specific firms such as Colgate and Dulcolax devise and execute marketing strategies that cater to different genders. Through this study, I aim to understand the rationale behind these strategies, how nudge theory factors into marketing, and how susceptible female consumers can become through this marketing. I also aim to assess the general awareness of the public regarding the Pink Tax and to dissect a couple of Pink Marketing startageies adopted by firms to increase consumerism.

Methodology–Aim of the study

There are 2 primary aims of the study. The first aim is to assess the general awareness amongst the general public of Singapore regarding the Pink Tax. The second aim is to understand how and what features of the packaging of a product and it’s advertisement make women more susceptible to paying the Pink Tax.

Research Design

This study is an exploratory study. This study aims to further investigate the various reasons as to why women make these consumer decisions. This is done so via surveys which consist of general questions to assess overall awareness and incorporates 2 case studies in order

to make sense of consumer rationales. This study does not aim to establish causality or make generalizable conclusions. Instead, it serves as a starting point for further research and can guide the development of more focused studies, such as descriptive, correlational, or experimental studies, which can provide more conclusive evidence and conclusions.

Consent and Ethical Issues

All ethical considerations were kept in mind during the course of the study. Participants were made completely aware of the fact that the data from their responses would be extracted and used to formulate general trends and claims. Moreover, no identifier information, such as but not limited to: name, contact details, and photograph, was collected. Only age bracket and details on gender were collected in order to draw conclusions based on different demographics. However, providing information on the participants gender was completely optional. Furthermore, confidentiality and privacy of the respondents was maintained, and the data has not been, and never will be disclosed to a third party. All the ethical guidelines of research were followed.

Sample

All respondents were residing in Singapore. The survey was conducted in english, therefore all respondents are fluent in Standard English. Data was collected from a total of 35 respondents.

They were from various age brackets as depicted below:

Age Bracket	**Count**	**Percentage**
13-19 31-40 41-50 51-60	3 10 20 2	8.6 28.6 57.1 5.7
Gender	**Count**	**Percentage**
Female Male	27 8	77.1 22.9
Total	**35**	**100**

Table 1: Demographic details regarding chosen sample

Data Collection Procedure

In order to collect data which was sufficient to assess whether one is aware of the concept of the Pink Tax or not, a Google Form was created in the form of a quiz. Questions ranged from

open ended questions to multiple choice questions. The form consisted of one general response section in which respondents were asked general questions regarding the Pink Tax. The following 2 sections were based on case studies. The first case study was about Dulcolax's stool softener in which there was a slight product differentiation in terms of the different symptoms they were each made to treat. The second case study was regarding Colgate's Omron electric toothbrushes. No difference in product existed here, except the colour of the brushes and packaging. One was black and one was pink. Respondents' general awareness regarding the subject of the Pink Tax is going to be measured quantitatively. Furthermore, the responses of women who chose the pink version of the product, are going to be analysed qualitatively in order to get a glimpse into the marketing strategies firm use to promote pink products to women.

Results and Discussion

In this section, the overall level of awareness regarding the pink tax, including the percentage of respondents who were familiar with the concept and those who were previously unaware of its existence in presented. Subsequently, qualitative findings, which provide insights into the various motivations influencing women's selection of pink products are presented.

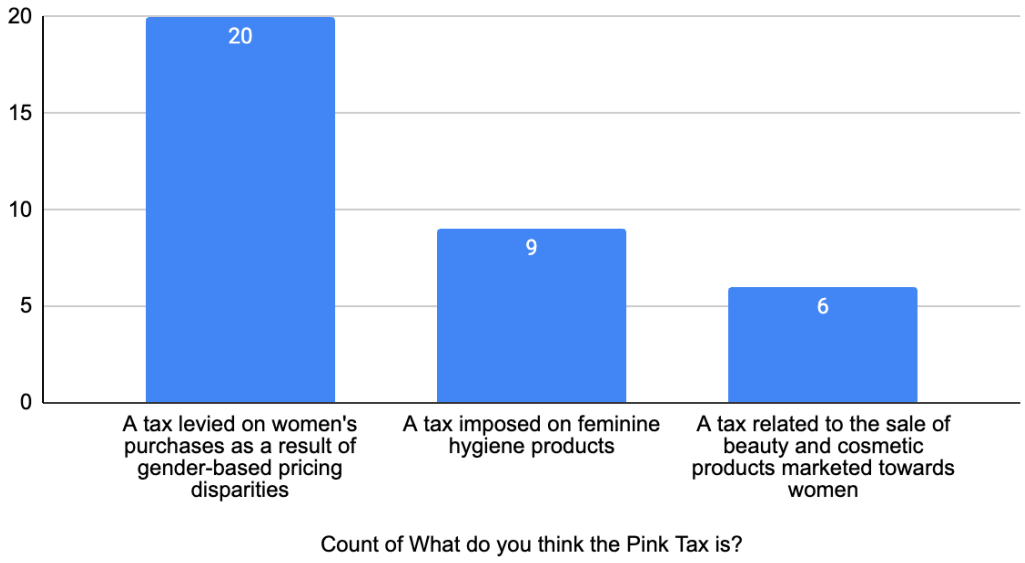

Figure 1: *Graphical representation of ratio of respondent's responses of what the Pink Tax is (N= 35)*

The first question related to the Pink Tax on the questionnaire was "What do you think of the Pink Tax?" The correct answer was "A tax levied on women's purchases as a result of gender-based pricing disparities". 20 out of 35 respondents, which is equivalent to approximately 57.1% of the respondents got the answer right. 9 out of 35 respondents, or approximately 25.7% of respondents believed that the Pink Tax was simply a tax imposed on feminine hygiene

products. 6 out of 35 respondents, or approximately 17.1% of respondents thought that the Pink Tax was a tax related to the sale of beauty and cosmetic products marketed towards women.

By analysing these results, we can understand that just above 50% of the sample size is aware of what the Pink Tax is. By further analysis, a common misconception that manifests in almost half the respondents minds is that the Pink Tax only prevails in certain industries like the beauty and wellness industry. However, this is not true. The Pink Tax exists in almost every industry such as the retail industry and the manufacturing industry.

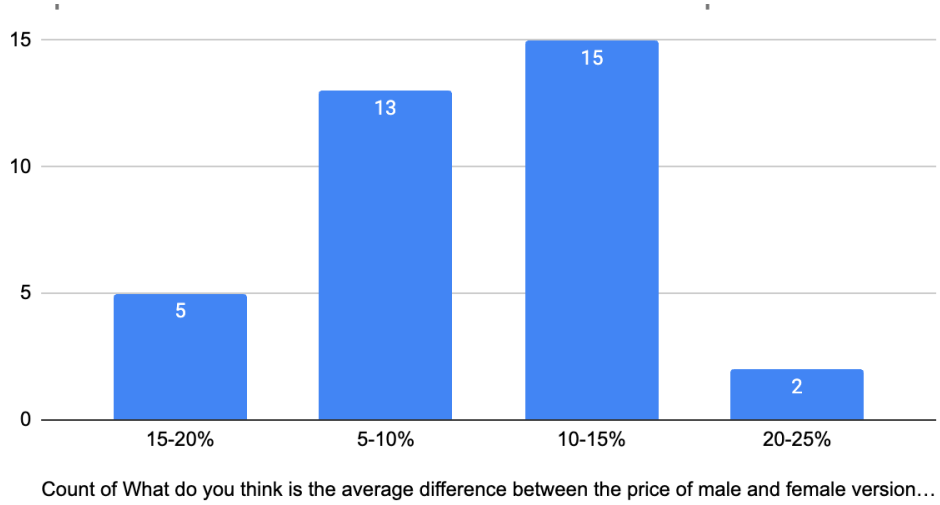

Figure 2: *Graphical representation of ratio of respondent's estimate of the average difference in price of male and female versions of products (N= 35)*

On average, DCA found that women's products cost 7 percent more than similar products for men (Gender-pricing-study, n.d.). However, based on the responses to this question, it doesnt seem as though a lot of people are aware of this. Only a mere 37.1% of respondents got the correct answer to this question, showing the lack of general awareness regarding the Pink Tax. Respondents seem to be overestimating the price difference between products which have different versions for men and women.

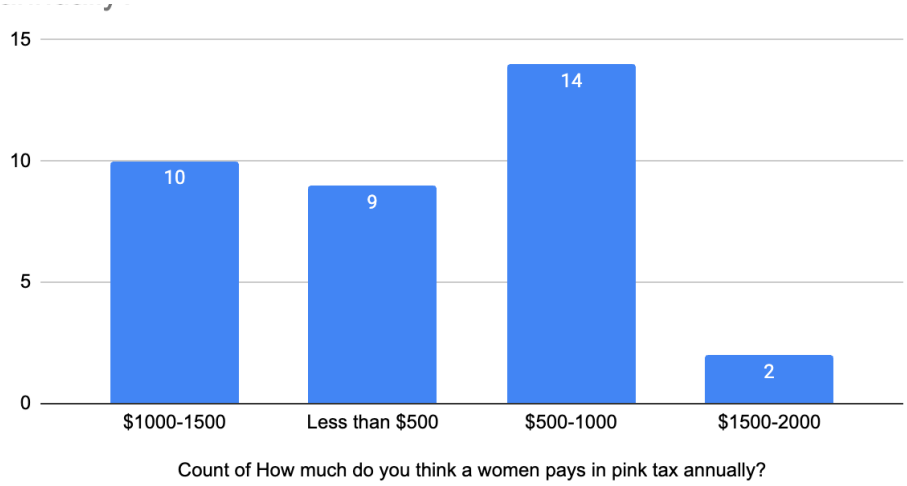

Figure 3: *Graphical representation of ratio of respondent's estimate of the amount a women pays in Pink Tax annually (N= 35)*

On an average, women pay around 1300 US Dollars in Pink Tax annually. (2023) Again, not many people seem to be aware of this fact. A mere number of 10 respondents, which corresponds to 28.6% got the answer correct. 23 respondents, or 65.7% understated the amount to be between 0-1000 USD, whereas 2 respondents, or 5.7% overstated the amount to lie between 1500-2000 USD. The next section will assess how many people got all 3 questions regarding the Pink Tax right. Ie. The people who are well informed regarding the subject and its manifestation. Only responses from respondents who displayed a general understanding of the concept of the Pink Tax, as depicted by the first question will be analysed. 20 responses are being analysed in this section.

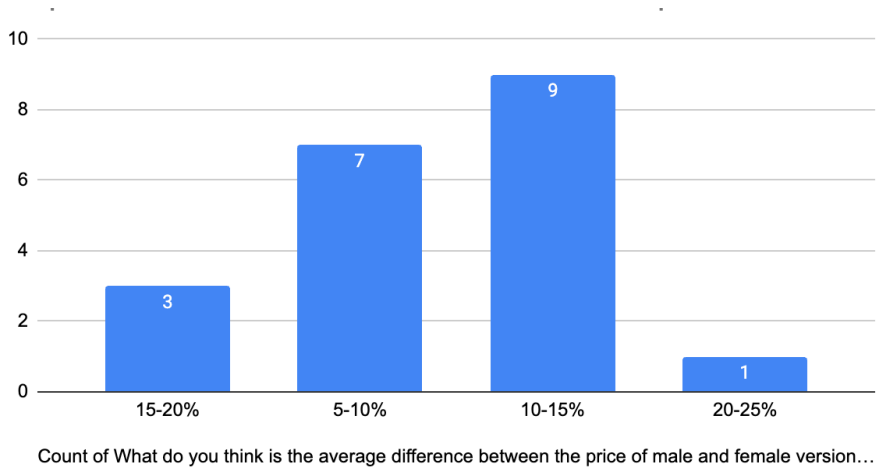

Figure 4: *Graphical representation of ratio of 20 respondent's estimate of the average price difference in products due to the Pink Tax (N= 20)*

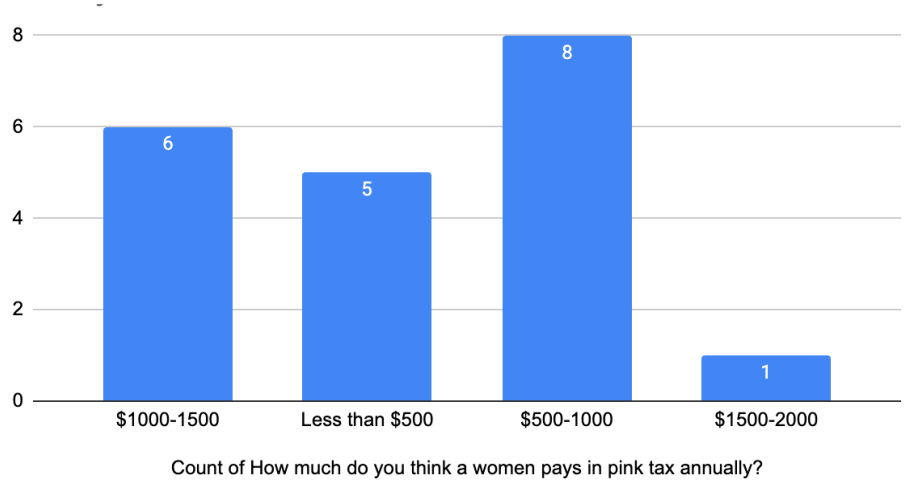

Figure 5: *Graphical representation of ratio of 20 respondent's estimate of how much a woman pays in Pink Tax annually. (N= 20)*

Out of 20 respondents, there was only 1 respondent who got the answer to both the following questions right. This means that only 1 out of 35 respondents displayed thorough knowledge and awareness regarding the Pink Tax. The findings of the exploratory study on the pink tax revealed a disheartening level of awareness among respondents, with only 2.9% demonstrating a perfect understanding of this pervasive issue. Despite the growing discourse surrounding gender-based pricing disparities, the majority of participants displayed limited knowledge or misconceptions regarding the pink tax. The study's findings underscore the importance of ongoing research and advocacy efforts to address the pink tax, as it remains a relatively unknown and misunderstood phenomenon in the wider population.

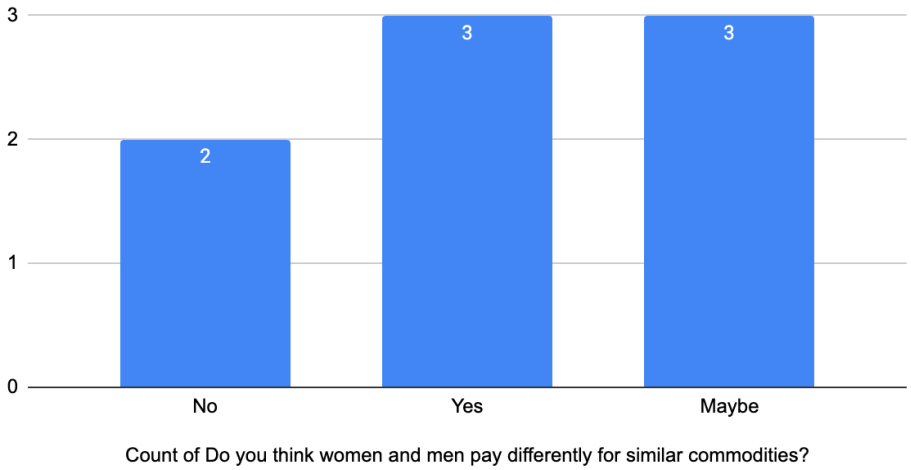

Figure 6: *Graphical representation of men's responses to the question stated above (N=8)* 3 out of 8 males, which corresponds to 37.5% are aware of the existence of the Pink Tax.

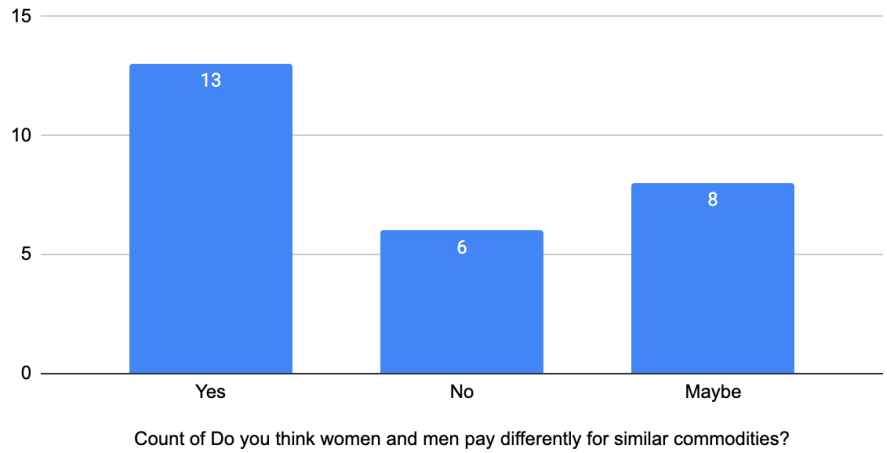

Figure 7: *Graphical representation of women's responses to the question stated above (N=27)*

13 out of 27, which corresponds to 48.1% are aware about the gender based price difference. In conclusion, the general awareness of women is higher as compared to that of men. General susceptibility of women to the pink tax: Here, the Colgate case study is being used as the only feature that differentiates the 2 products are their colours. 13 women picked the pink toothbrush over the black toothbrush. When asked why, a few reasons were given, which are stated below:

Reason for choosing the Pink product	**Count**
Preference for the colour pink	9
The product better serves the female gender	4
Total	**13**

Color psychology suggests that different colors can have an impact on our moods, feelings, and even behaviors. The color pink, for example, is thought to be a calming color associated with love, kindness, and femininity. The association between the color pink and femininity is largely a cultural and societal construct. Pink has been traditionally associated with femininity, while blue has been associated with masculinity. Many female consumers prefer the colour pink and are often willing to buy pink products even at a slightly higher price. Pink is often used in products targeting women to create a sense of femininity, softness, and delicacy. Advertisers and marketers have capitalized on these associations, using pink hues to evoke emotions and connect with their intended audience. 9 responses, all referring to the “better” colour and appearance of the brush display this.

The second type of responses is interesting. The consumer thinks that the product may have a few features that makes her consumer experience more enjoyable. The use of the colour

pink has also gotten a consumer to believe that the pink product, in comparison to the black, offers something more or extra to women to enhance user experience. However, this is not that case and simply makes women more susceptible to the pink tax.

Conclusion

This research paper aimed to investigate the influence of marketing and advertising strategies on buyers and their contribution to the prevalence of the Pink Tax. Furthermore, data was analyzed in order to produce statistics showing the general awareness of the public regarding the Pink Tax.

It was found that while around 57.1% of respondents were aware of the Pink Tax, only 2.9% of the respondents were completely aware of this concept. This underscores the need to raise awareness of this gender-based pricing technique.

Furthermore, a quick insight into womens susceptibility to the Pink Tax revealed that cultural and social influences, combined with firms' strategic marketing can make women more susceptible to the Pink Tax. Society often associates pink with femininity and girls from a young age. Stereotypically, girls are given pink toys and clothing, which can contribute to the perception that pink is a "girly" color. These cultural and social influences can shape preferences over time. Furthermore, companies often use gendered marketing strategies to target specific demographics, including women. Pink is frequently used in marketing campaigns targeting women and is associated with products in traditionally feminine categories, such as cosmetics, fashion, and self-care. This can reinforce the association between women and pink products.

The implications of this research are multifold. First and foremostly, it emphasises the importance of raising awareness and scrutinising marketing and advertising practises that contribute to the Pink Tax. Policymakers and consumer advocacy groups can address and mitigate gender-based pricing discrimination by recognising the role of these techniques in perpetuating it.

Secondly, this research contributes to the existing literature on the Pink Tax and its sociocultural implications. It contributes to our understanding of the intricate interactions between marketing, advertising, gender norms, and consumer behaviour. Our research gives a thorough picture of the Pink Tax phenomena and its underlying drivers by examining the ways through which marketing influences customers.

Limitations

It is essential to acknowledge the limitations of this study to identify areas for future research. The research was conducted within the specific geographic region of Singapore and may not fully capture the nuances of the Pink Tax phenomenon across diverse cultural contexts. Future studies should strive for broader geographical representation to examine the extent of gender-based pricing discrimination globally.

Secondly, the sample size used for this study was limited to 37 respondents. A larger sample size may provide a more accurate insight into the general awareness about the Pink Tax and women's psychological tendencies when it comes to making purchases.

Lastly, the research predominantly utilized quantitative methods, limiting the depth of insights into individual experiences and perceptions. Incorporating qualitative approaches, such as interviews would provide a more in-depth understanding of the emotional and psychological impact of marketing and advertising strategies on buyers.

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The Effects of Virtual Reality Therapy on Patients with Alzheimer's Disease By Dhivya Muthupalaniappan

Abstract

This paper investigates how effective virtual reality therapy can be as a treatment option for patients with Alzheimer's disease. It has been hypothesized that under stimulation of the brain could possibly be correlated with developing Alzheimer's, but virtual reality might be able to bridge this gap since it continuously gives the brain interesting tasks to do. The following is a literature review analyzing three recent studies that are described in the methodology and results sections of this paper. These studies assess either the: cognitive benefits, comfort level, or social emotional effects of virtual reality, and they show that virtual reality, or VR, may have the potential to improve cognitive function in those with Alzheimer's disease while also being comfortable to use. If larger studies assessing this same concept are completed in the future, VR does have the possibility of becoming a treatment option to Alzheimer's patients in the coming years.

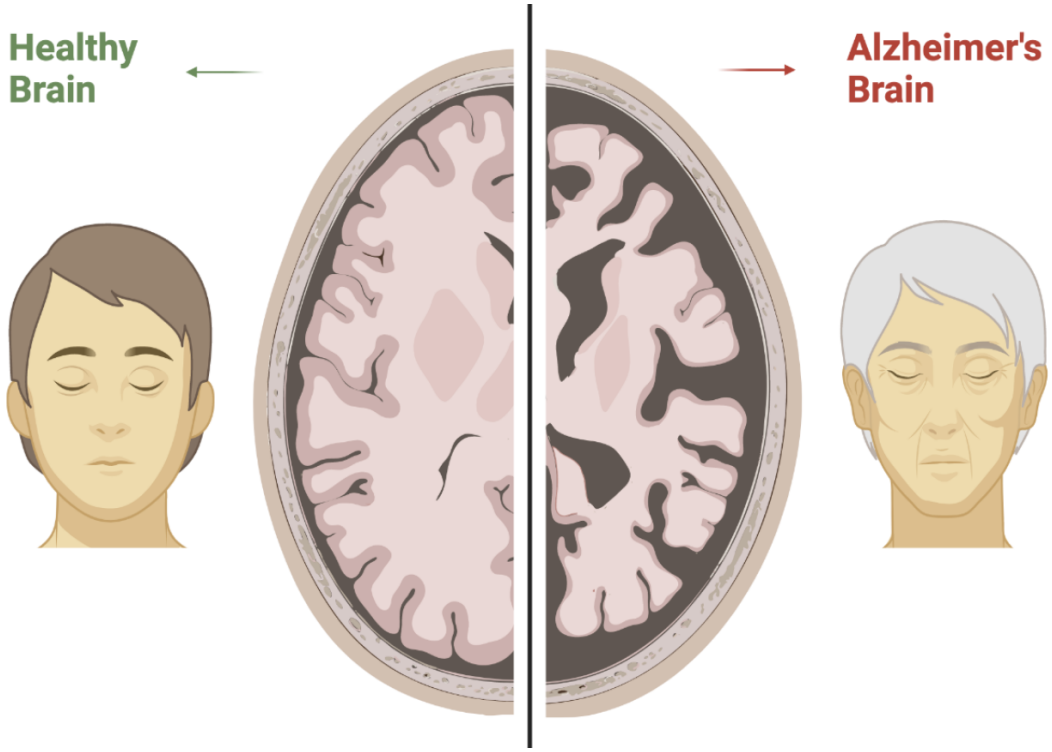
Introduction

While virtual reality technology may be a fun activity for people of all ages to do, it might have a larger impact than this since it could be on the way to help treat major diseases like Alzheimer's. Alzheimer's disease is a complex neurodegenerative disorder that affects 1 in 9 people over the age of 65, and an increasing number of researchers and scientists are starting to experiment with and dissect this disease. Currently, there are a little over 215,000 papers about Alzheimer's disease on PubMed indicating the large interest in understanding and treating this disease.

In Alzheimer's disease, patients are prone to forget things and can experience numerous other symptoms from behavioral problems to being unable to speak or express their thoughts in any way. Since the general life expectancy of humans is increasing, the amount of people developing diseases like Alzheimer's in their older ages is also increasing. Currently though, there are no known ways to slow down the progression of Alzheimer's, let alone find a cure. Virtual reality is one of the approaches being explored to determine its efficacy as a treatment for Alzheimer's patients.

Since virtual reality is an immersive, exciting experience for anyone, especially older adults in the age range for developing Alzheimer's disease, it has the potential to provide them with a challenging experience that may have therapeutic effects on brain function. When the brain is active, it can then be hypothesized that virtual reality therapy might be able to improve cognitive functions by providing virtual stimulation.

Figure 1.
Healthy Person's Brain vs. Alzheimer's Patient's Brain (created and copyrighted by Dhivya Muthupalaniappan)



Background Information

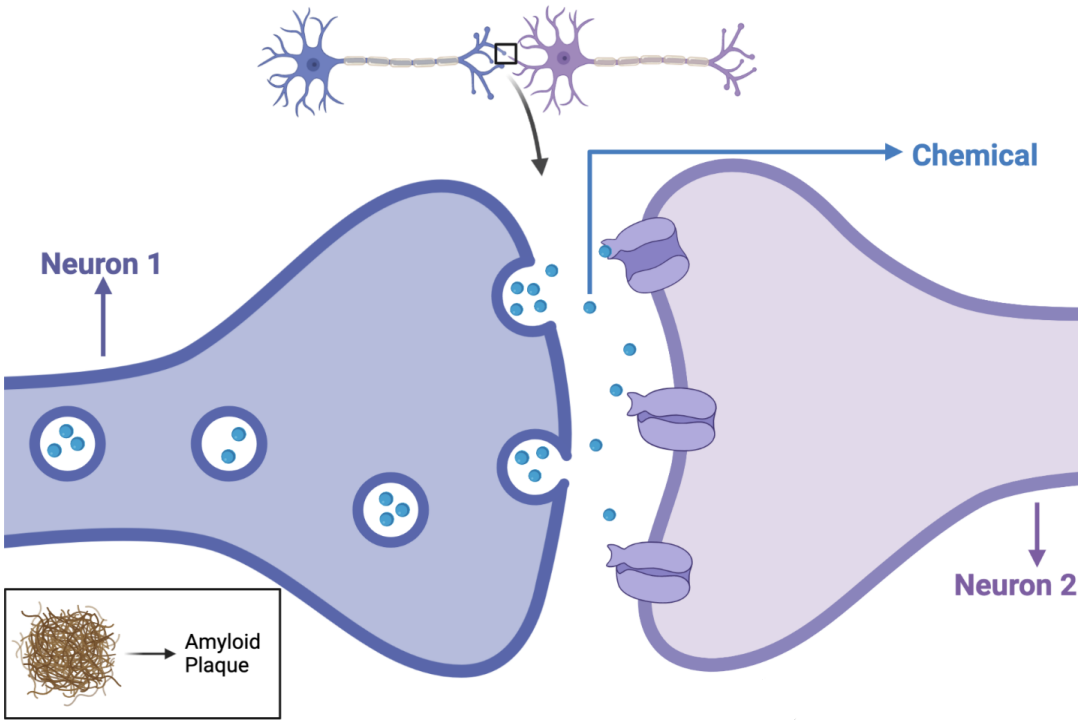
Alzheimer's was first identified and diagnosed by Dr. Alois Alzheimer in the early 1900s. When two women who shared similar symptoms died, he noticed that their brain tissues seemed to be different from those of others, and after close consideration, he concluded that they both had the same disease. These women's symptoms included memory loss, unpredictable behavior, and language problems, and the two also had abnormal plaques and tangles of fiber in their brain, now called amyloid plaques and tau tangles, and brain atrophy due to the death of neurons. These histopathological hallmarks are still currently the main indicators that a person has this disease. From then though, the progression of research done on Alzheimer's has given us much more background than we had a century ago, but there are still many more things to learn.

Healthy Brain

The brain processes information through the activity of nerve cells, or neurons, traveling all throughout the body to deliver messages. They do this by continuously communicating electrochemically; Electrical charges called action potentials pass along long neuronal processes called axons. When the action potential reaches the end of the axon, the neuron passes on the message by releasing chemicals called neurotransmitters through tiny gaps between neurons called synapses. Neurotransmitters cross the synapse and elicit electrical signals in the postsynaptic neuron, and, if needed, these electrical signals may summate to elicit a new action potential in the next postsynaptic neuron to continue passing on the brain's message.

As the neurons are transferring messages between each other, other important brain cells including astrocytes and microglia take care of them and their environment by keeping the brain clean. They dispose of the waste and dead or damaged brain cells to keep everything in order and functioning to the highest extent.

Figure 2.
Neurons Transferring Messages (created and copyrighted by Dhivya Muthupalaniappan)



Alzheimer's Brain Differences:

However, in a patient with Alzheimer's disease, the process stated above is impaired. Two proteins in the brain, beta-amyloid and tau (also mentioned above) somehow become toxic to the brain and form abnormal clumps for an unknown reason. The amyloid plaques and tau tangles that are formed are primary indicators of Alzheimer's, and disrupt neuronal processes, eventually leading to synapse loss and neuronal death. This is what eventually causes people to have hardships while completing their daily tasks.

The beta-amyloid plaques start building up and forming years before any signs of Alzheimer's dementia even show, and they gradually destroy synapses and neurons, ultimately impairing large scale information processing necessary for normal cognitive function and health.

Figure 3.
Tau Tangles/Neurofibrillary Formation (created and copyrighted by Dhivya Muthupalaniappan)

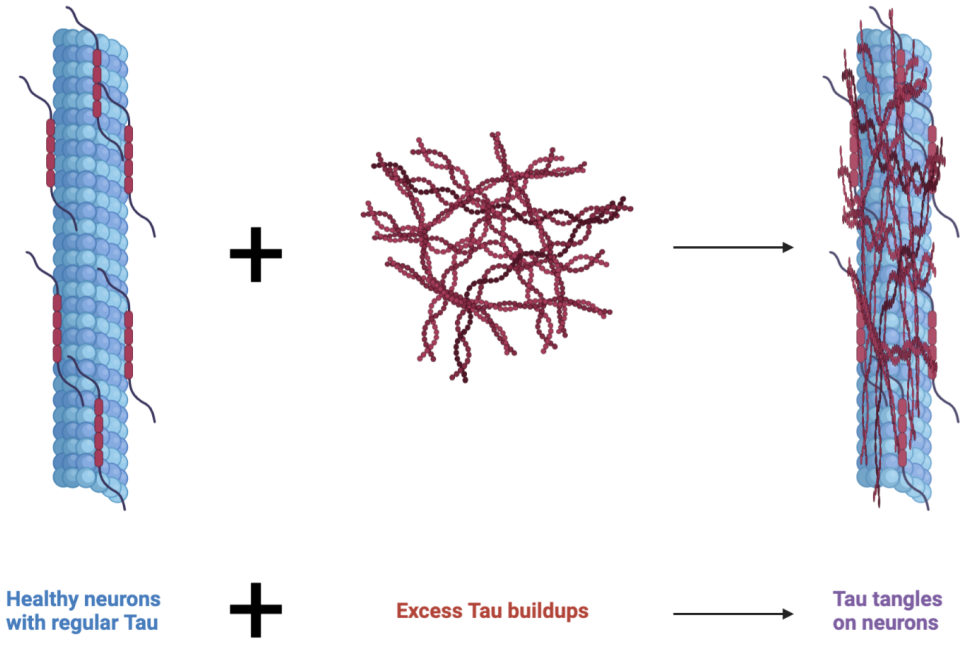
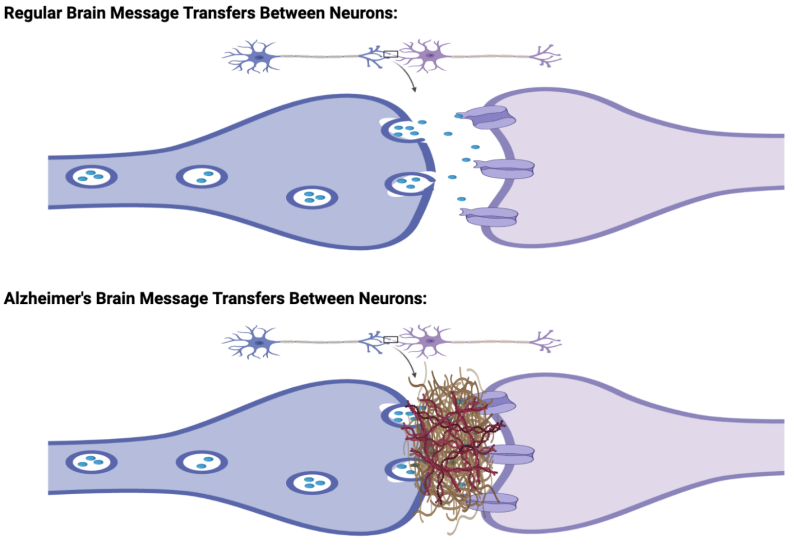
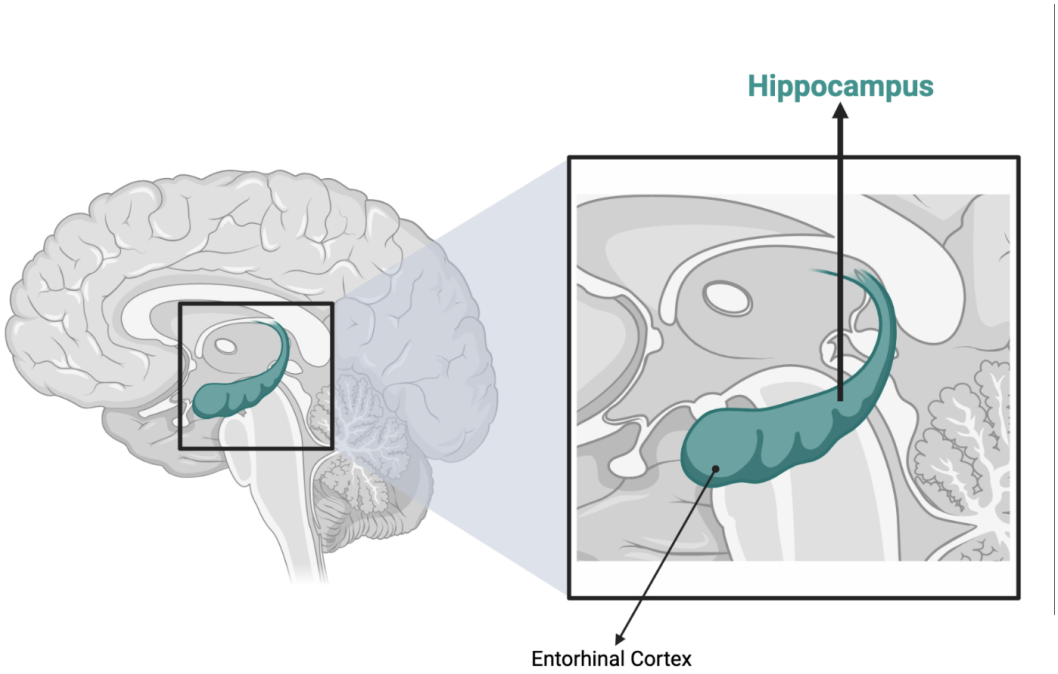


Figure 4.
Regular Brain Message Transfers vs. Alzheimer's Brain Message Transfers (created and copyrighted by Dhivya



Eventually, neuronal loss is sufficient to cause the brain to shrink. The process in which the brain tries to maintain the 'status' or state it is in is called homeostasis, but when these the beta-amyloid and tau proteins build up an excessive amount and the brain is unable to clean them out, it is not able to maintain homeostasis, which causes the brain to deteriorate. This process starts in the hippocampus and entorhinal cortex of the brain, the parts that form memories, so memory loss is often a common early symptom. As the stages of this disease progress though, more and more of the brain shrinks and a person starts to have more difficulty doing tasks they previously used to do quickly and efficiently.

Figure 5.
Hippocampus & Entorhinal Cortex Location in Brain (created and copyrighted by Dhivya Muthupalaniappan)



Because this disease affects so many people, it's the 7th leading cause of death in America, researchers are actively searching for biomarkers and ways to predict this disease early on. Biomarkers are known as indicators or early changes that show a disease might be present in someone through medical scans and procedures such as brain imaging, cerebrospinal fluid testing, and blood testing. In addition, the earliest symptoms of Alzheimer's disease include: memory problems, word-finding issues, vision/spatial issues, and impaired reasoning or judgment, so doctors try to catch these as early as possible. If an accurate way to predict Alzheimer's does come about, it may save an immense amount of lives by enabling the discovery of prophylactic treatment which can stop a disease in its early stages.

Stages

The three stages of Alzheimer's progression are summarized as follows; One who has memory loss, gets lost easily, has trouble handling money, and takes longer to complete daily tasks usually has mild Alzheimer's, the first stage. At this point, people will usually get diagnosed after close family members and friends start realizing changes in their personality and take them to a doctor. If the first stage goes unnoticed though, people are usually diagnosed by the next stage, moderate Alzheimer's.

Now, parts of the brain that control language, reasoning, thoughts, and sensory processing (ability to detect smells and sounds) would be damaged too, and memory loss worsens to where the patient might potentially have trouble recognizing family and friends. Furthermore, the patient may also react with impulsive behavior, be unable to learn new multi-step tasks, cope with unfamiliar situations, or have hallucinations, delusions, or paranoia.

Finally comes the last stage of Alzheimer's by which people are already diagnosed; Along with all of the previous symptoms, patients in this stage of the disease are completely dependent on others for their care, cannot communicate, stay in bed most of the time, and are nearing the end of their lives. Usually, after the initial diagnosis occurs, patients live for about 10 more years on average at a hospice care, but as every patient differs, the life expectancy could be anywhere from 3 to even 20+ years.

Loneliness' Effect

Alzheimer's is also associated with persistent loneliness according to several studies. Some believe that feeling lonely can cause impairment in social skills, and this can lead to cognitive decline which is associated with brain atrophy. In a study done by *Neurology* in 2020, loneliness is defined as feeling lonely 3 or more days per week. A quick overview of the study is provided below.

This study was published on February 7th, 2020 and 2,300 healthy participants who were dementia-free and genetically low-risk for Alzheimer's participated. All of the participants underwent cognitive tests and MRI (magnetic resonance imaging) scans around 2010. Ten years later, participants were reassessed in 2020 and 22% of the lonely participants developed Alzheimer's, and 13% of the not-lonely participants developed Alzheimer's as well. Overall, it was concluded that loneliness and the brain atrophies associated with Alzheimer's may be related.

Current Cause Theories

The cause of Alzheimer's is unknown and it is unclear whether loneliness is a cause or an effect of the disease. Some of the other common theories regarding the cause of Alzheimer's include genetic mutations or hereditary causes, environmental factors, lifestyle factors, and the presence of a protein called Apolipoprotein 4 (APOE4) on the 19th chromosome. Although having APOE4 doesn't directly cause Alzheimer's, researchers have found that having this allele significantly increases a person's risk.

Diagnosed, Next Steps:

When an Alzheimer's patient and their close family or friends first talk to a doctor about any symptoms they have noticed, the doctor typically starts out with simple memory, problem-solving, attention, counting, and language tests, then moves on to standard blood tests. If needed, they might even prescribe brain scans like CTs, MRIs, and PET scans. By doing these things, the doctor can determine whether the symptoms the patient shows are actually due to Alzheimer's or are the symptoms of another condition or disease presenting similarly to Alzheimer's disease.

Following this, the doctor may then prescribe the approved USFDA (United States Food and Drug Administration agency) medications. These are medicines such as Donepezil, Memantine, Rivastigmine, and Galantamine for mild to moderate cases of Alzheimer's, and a Donepezil and Memantine combination for severe cases. While these medications might help with regulating neurotransmitters (by which neurons transmit messages at synapses) and sometimes reduce behavioral problems, they do not actually change the underlying process causing Alzheimer's and can be ineffective for some patients. The only two medications approved to treat the underlying process of Alzheimer's as of right now are Aducanumab and Lecanemab; These medicines help reduce amyloid plaques so they may help slow the progression of Alzheimer's.

Virtual Reality Enters the Equation

This is where virtual reality starts to come into play; Although it is unlikely to slow the underlying disease process of Alzheimer's, researchers are evaluating whether it can manage symptoms like loneliness while possibly improving cognitive function. The best part about virtual reality is that it is non-invasive and therefore minimizes the risks of drug-related side effects and toxicity to the body. Virtual reality is just something one experiences while wearing an HMD (head mounted device).

Other common names for virtual reality may include: cyberspace, augmented reality, artificial reality, and telepresence. These systems refer to the ability to interact and feel immersed in a nonexistent setting so that the user becomes completely unaware of their real surroundings and more aware of their virtual ones. The reason one feels fully immersed in these artificial settings is because they seem so falsely real. Developers use as many components that are in the real world as possible such as 360 vision and head-tracked audio and are even trying to implement a sense of touch too to make the experience as believable as possible.

Many things come into play while manufacturing virtual reality devices though; Users are very fast to identify when a VR experience diverges from a real experience with one indicator being the amount of latency or lag time between a user's actions and a computer's outputs. Studies show that even if a computer is more than 50 milliseconds off from when a user performs an action to the output happening, it is detectable and reduces the feeling of immersion the user previously felt. They also show that at least 20 - 30 frames must be produced per second

to make the experience convincing. Manufacturers have found solutions to all of these problems and the resulting products are now useful both for entertainment and possibly for medical purposes too.

Researchers have hypothesized that virtual reality could help patients with Alzheimer's disease by providing a form of cognitive remediation or by stimulating synchronized patterns of brain activity that are decreased in patients with Alzheimer's. Additionally, many published studies have provided promising evidence that virtual reality may be well tolerated and potentially beneficial to patients with Alzheimer's disease.

Methods/Result

The studies analyzed below are selected from a wide range of papers available on PubMed. While doing a search for these studies, the most common search term used was "Alzheimer's; virtual reality feasibility studies" and the three studies below were chosen from the 5 studies available for public access, from the 11 results. These studies were particularly chosen since they measured the efficacy of virtual reality through baseline and post-therapy assessments making them comprehensive and analyzable.

Study 1 (Hofmann 2003):

Methods

9 age and gender matched patients who all had Alzheimer's disease and 10 healthy control subjects participated in a study in 2003. Their task was to navigate their way through a virtual reality grocery store to get 3 items along with answering 10 multiple choice questions about the journey. The accuracy rates from each of these tests were measured by calculating the number of times a person went the accurate way in the grocery store, the time they took to receive the items, and the number of correctly answered questions on the test. After the pre-test was conducted for everyone, they also underwent 12 VR training sessions over the course of 4 weeks before taking the post-test.

Results

Results from this study concluded that while virtual reality was indeed beneficial to Alzheimer's patients, it was helpful to the healthy control subjects as well. Initially, Alzheimer's patients performed significantly worse than the healthy participants and had a much higher number of mistakes in both parts of the tests, but after the VR sessions, all participants performed better on the post test with the Alzheimer's patients improving the most. They were also able to retain these improvements for the 3-week follow-up session as well. In addition, self-reported feedback showed that all of the participants enjoyed the immersive VR experience, and it was concluded that VR's potential beneficial effects on cognitive function should be tested further

Study 2 (Aruanno 2019):

Methods

The HoloLens tools by MemHolo is an HMD (head mounted device) that was designed especially for the use of Alzheimer's patients; Its activities include short-term memory and spatial reasoning practice games to help prevent cognitive decline in those with Alzheimer's disease. In this study, patients used this device to first play these games alone, and then also in groups of 2 or 3 people. This study started with the inference that virtual reality was already helpful for patients with Alzheimer's disease and was primarily conducted to evaluate potential improvements of the VR devices themselves.

Results

According to feedback from the patients, the device worked well for everyone, except one female participant who wore glasses. She claimed to have difficulty seeing since the device didn't fit properly on her head, and she found that it impaired her experience. In addition, to analyze the difference in behavior of participants while they played alone vs. with others, it was observed that people helped each other when with others showing that the MemHolo Lens can encourage social behavior.

Study 3 (Mendez 2015):

Methods

Five patients who all had Alzheimer's disease underwent 2 types of interviews; One of which was conducted by a human interviewer, and one of which was conducted through an avatar in a virtual reality setting. The answers were recorded in both scenarios and evaluated at the end. This study sought to measure the difference in the patient's responses in these two settings.

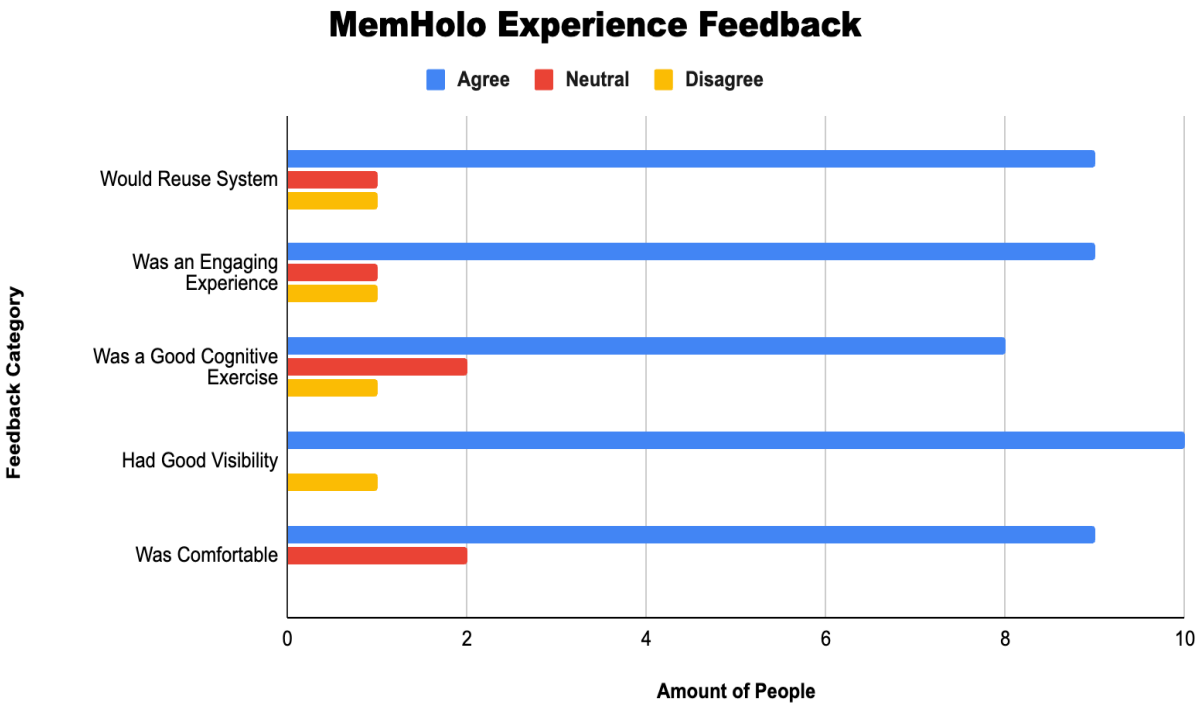
Results

It was concluded that all 5 participants provided more detailed responses and were more 'open' and talkative in their virtual interviews as compared to their real ones with humans. These observations suggest that virtual reality experiences might also elicit more social-emotional behavior from those with Alzheimer's.

Discussion

The consensus of the studies reviewed here is that virtual reality offers potential benefits to Alzheimer's patients and is a positive experience for patients with this disease. The results from one such study, the use of MemHolo Lens to help with Alzheimer's (study 2 of this paper), are shown below:

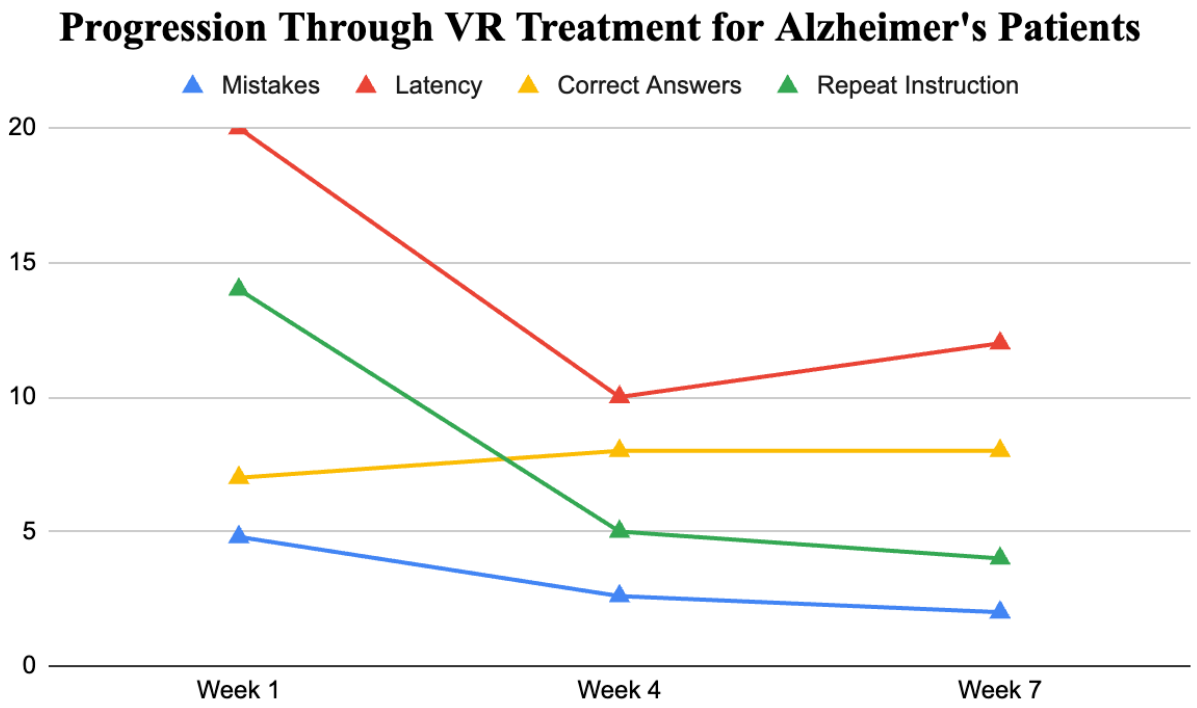
Figure 6.
MemHolo Lens Virtual Reality Experience Feedback (Study 2) (created and copyrighted by Dhivya Muthupalaniappan)



Through the feedback given, researchers concluded that the MemHolo Lens was comfortable, and most people liked the VR experience, which may improve compliance with a potential virtual reality treatment regimen.

While these studies suggest virtual reality is well-tolerated, other studies focused on its potential efficacy to improve cognitive functions by comparing a patients' baseline performance with that of their performance over the course of numerous virtual reality treatments. In this paper, study 1 analyzes this factor and the changes shown through the treatment are shown in a graph below:

Figure 7.
Progression of Various Factors Through Virtual Reality Treatment in Alzheimer's Patients (Study 1)
(created and copyrighted by Dhivya Muthupalaniappan)



"Mistakes" is the first of 4 categories, and it refers to the number of incorrect responses to a prompt in the virtual reality activity. (An example is shopping for a list of items and turning down the wrong aisle based on the signs in a virtual grocery store.) As seen while following the path of the blue line, the number of mistakes goes from about 4.8 to 2.6 to 2 throughout the seven weeks, showing a small improvement.

The next category, "Latency", refers to the amount of time it took to complete an activity on average. The latency starts high at 20 minutes, but then decreases down to half of that at 10 minutes which is an improvement that was maintained. This shows that as patients became familiar with a VR task, they took less time to complete it.

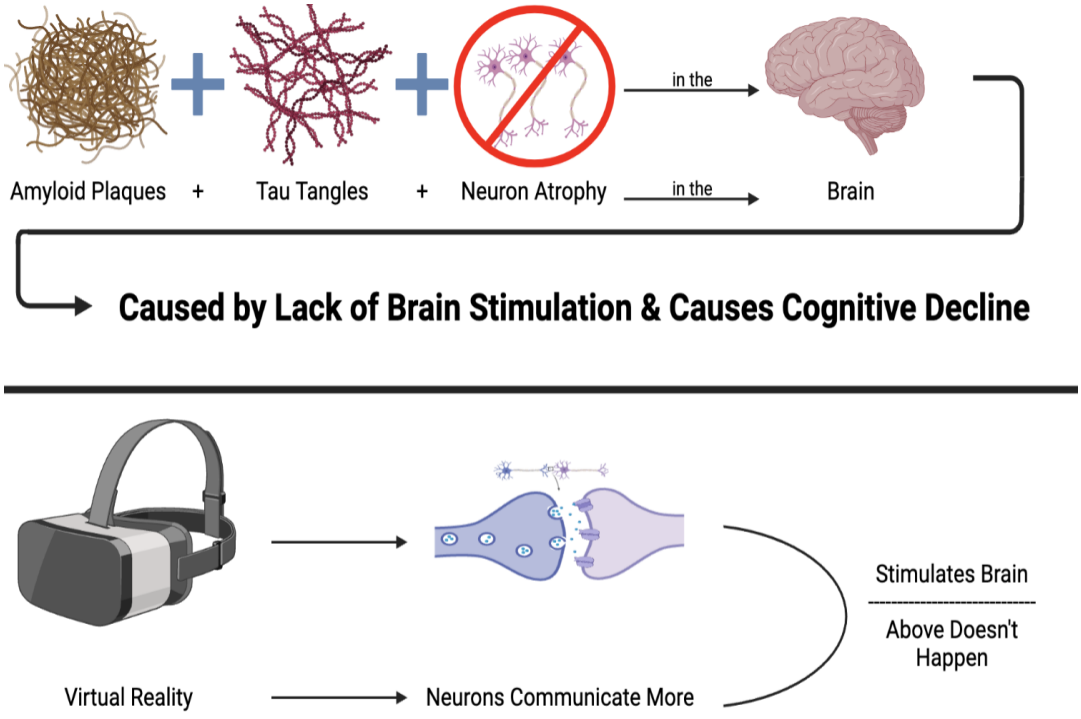
After "Latency" comes "Correct Answers" which simply assesses the number of correctly answered questions in the multiple choice test given directly after the VR activity. Since this tests the patient's ability to remember things, it is an important factor in the study. As shown, patients exhibited a small improvement in their potential to recall things over the course of their VR treatment. They start by answering about 6.5 of the questions right in week 1, but answer about 8 questions right in the following weeks. Although this change wasn't major, more consistent training sessions and a longer amount of VR usage could possibly produce a more significant difference.

And finally comes “Repeat Instruction” which counts the amount of times the patient may have forgotten what their given task was and asked for the directions to be stated again. As seen above, this number greatly drops between the first two points, and continues decreasing from the second to the third as well. Overall, the numbers go from 15 to 5 to 4 which shows major improvements in this category.

Additionally, study 3 (Mendez, 2015) evaluated the potential of VR to improve the social emotional interactions of patients with Alzheimer's disease. This study found that patients were more detailed and clearer in their answers to their virtual avatar interviews rather than to their interviews with a real human being. This intriguing result suggests the potential usefulness VR holds when it comes to social emotional difficulties often encountered when interacting with Alzheimer's patients.

Furthermore, to revisit the hypothesis stated at the beginning of this paper (a lack of brain stimulation possibly causing cognitive decline which is a major indicator of Alzheimer’s disease), it is now seen how virtual reality fits into and potentially affects this sequence. A depiction is provided below:

Figure 8.
Alzheimer’s Disease Process/Progression
(created and copyrighted by Dhivya Muthupalaniappan)



In conclusion, the graphs and studies explained above suggest that virtual reality may be a promising treatment option for patients with Alzheimer’s disease. These results are consistent

with the hypothesis that virtual reality may evoke patterns of neural activity that are decreased in Alzheimer's and therefore help to maintain brain health.

Study 1 suggests that VR therapy may improve cognitive function. Study 2 showed that VR is a comfortable and engaging experience that patients may be willing to continue with as a treatment option. And lastly, study 3 suggests VR may increase social behavior in Alzheimer's patients.

The studies reviewed here indicate that further research should be conducted to evaluate the efficacy and safety of VR therapy for patients with Alzheimer's disease. Such studies could evaluate the optimal VR protocol as a treatment for Alzheimer's. Much larger and longer-duration studies will ultimately be necessary to determine whether VR is an effective treatment option, and the magnitude and durability of improvement that VR therapy may offer.

All in all, virtual reality appears to have a positive effect on patients with Alzheimer's disease and it may be beneficial to them as a possible treatment option in the future. It is critical that further research is conducted to follow up on these promising results to further investigate the effects of virtual reality therapy.

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The Rise of Autism: Causes and Diagnostics By Mila Sonkin

Abstract

Autism Spectrum Disorder (ASD) is becoming increasingly common in individuals today. The reason for this could be that clinicians are either extremely improving our diagnostic methods or autism is just becoming more prevalent due to various contributing elements. Furthermore, in addition to the specific screenings and evaluations that are used to identify autism, researchers are developing more and more tests that serve as useful tools for diagnostics. This study compiles several different factors linked to autism, addresses some theories that have stated a connection to autism, and explains the current ASD diagnosis process and new diagnostic methods. The contributing factors explained in this study include genetics, specific genes, the environment, biological factors, neurological factors, the gut microbiome, and more. Considering that there is a significant number of causes of autism and currently a multitude of conjectures regarding what is actually linked to autism, this paper accumulates all of the data in an organized manner and clears up any confusion.

Introduction

Dr. Stephen Shore, a special education professor at Adelphi University, once said, "If you've met one person with autism, you've met one person with autism." In other words, individuals on the spectrum each have different strengths and weaknesses. Some may find it more challenging to communicate and interact with others while others may experience little difficulty when having a conversation.

According to the latest CDC report, in twenty years, autism went from being identified in one out of one hundred fifty children to being identified in one out of thirty-six children (CDC). Autism Spectrum Disorder (ASD) is a developmental disability that results in social interaction impairments, communication difficulties, repetitive behaviors, and obsessive interests. Some common social interaction impairments include the lack of communication, eye contact, body posture, and facial expressions, which can lead to individuals on the spectrum struggling to develop relationships. In addition, some communication impairments are the repetitive use of the same language and the inability to initiate conversations, which suggests a lack of speech development. Lastly, some repetitive behaviors and interests include intense focus and preoccupation with certain parts of objects, recurrent body movements, and extreme inflexibility to changes to routine (Saringer).

Levels of Autism

Essentially, there are three levels of autism, which vary from mild to severe based on their behavior, their social skills, and how much support they need. To start, ASD level 1 is the lowest classification and these individuals need some support due to their lack of social interaction and organization skills. Next, those with ASD level 2 require a considerable amount of support; these individuals struggle to communicate verbally and possess repetitive behaviors and strong interests in particular subjects. Lastly, ASD level 3 is the most severe level, where

individuals require significantly more support than individuals with ASD level 1 or 2. In addition to having more extreme characteristics than those with ASD level 1 or 2, they ultimately experience more trouble communicating, displaying very limited social skills (Lane Regional Medical Center).

Main Causes of Autism

Current research shows that there are several different factors that lead to the development of autism.

Genetics

To begin, a huge contributing factor to ASD is genetics. Likewise, according to Saringer, "having a sibling with autism raises children's odds of being diagnosed as well — likely due to similar genetic backgrounds." Additionally, genetic disorders, including Rett syndrome, fragile X syndrome, and tuberous sclerosis are suspected to genetically add to the likelihood of developing autism. In Rett syndrome, there is evidence that suggests that high brain deterioration may lead to autism (Saringer). In addition, mutations in the FMR1 gene on the X chromosomes prevent gene expression and cause fragile X syndrome. As a result, the FMR1 protein being absent during brain development excites the neurons that are associated with the syndrome (Rura). Consequently, the overexcitement of the neurons from Fragile X syndrome is another factor that researchers believe contributes to the development of autism. Lastly, according to Saringer, "the TSC gene mutation found in tuberous sclerosis can cause autism if it occurs during critical junctures in brain development." In summary, researchers state that the genetic mutations found in these three genetic disorders often cause the development of ASD. Other genetic disorders that can increase the risk for ASD include phenylketonuria, chromosome problems, and neurofibromatosis. In addition, a genetic mutation of the MTHFR gene impeded the process of methylation. As a result, an essential antioxidant for the body called glutathione is produced less efficiently and effectively, which causes oxidative stress. Scientists believe that this mutation is a risk factor for autism. As stated by Saringer, "These are environmental factors, but it's believed that genetic factors make these problems more likely." Ultimately, if someone has a certain genetic mutation in one of their genes that may contribute to being diagnosed with autism, specific environmental conditions or circumstances may increase the likelihood of acquiring autism.

Likewise, there are more than one hundred genes on different chromosomes that contribute to the development of ASD and many people with autism have mutations in these genes. According to NIH, "most people with autism have different mutations and combinations of mutations," and not all people with autism have "changes in every gene that scientists have linked to ASD. Many people without autism or autism symptoms also have some of these genetic mutations that scientists have linked to autism." Therefore, specific combinations of mutations or mutations alone may cause symptoms of autism and control how severe those symptoms are. In other words, different genetic mutations may increase the likelihood of being diagnosed with

autism. Ultimately, by being susceptible to ASD due to genetic mutations, environmental factors might result in the development of autism (NIH).

Moreover, epigenetics is the study of how one's behaviors and the environment can lead to changes that affect the way their genes work. Epigenetic changes do not change DNA sequences but they change how they are expressed (Centers for Disease Control and Prevention). Ultimately, epigenetic changes in the womb can cause autism. As of now, the epigenetic changes linked to autism include maternal influenza infection, prolonged maternal fever, and maternal asthma during pregnancy, which implies that pregnancy is a critical period when brain development can be affected (Saringer).

Specific Genes

Additionally, research has shown that there are several genes that are involved in the development of autism. According to Mccall, "Six of these are called ubiquitin ligases and they're responsible for attaching molecular tags called ubiquitins to proteins." Likewise, some scientists believe that a huge factor that causes autism is a gene mutation that inhibits the proper function of an ubiquitin ligase. At Washington University, a few scientists tested this hypothesis. They used young mice and removed an ubiquitin gene called RNF8 in neurons in the cerebellum, which is a specific area of the brain that is affected by autism and plays an important role in language, movement, and attention. As a result, the mice that were missing the gene developed 50% more synapses than the mice that had the RNF8 gene, which ultimately impacted their ability to learn. Moreover, the researchers "trained the mice to associate a puff of air to the eye with a blinking light" in order to see if the mice without the RNF8 gene had lower motor skills. Overall, although a human with autism isn't the exact same as a mouse that doesn't shut its eyes when trained to, this study highlights an association between behavior and synapses (Mccall).

Furthermore, one recent investigation looked at the DNA of more than 35,584 people worldwide, which included 11,986 autistic individuals. Subsequently, the scientists identified variants in 102 genes that were linked with an increased probability of developing autism. In addition, 53 of the genes identified were predominantly associated with autism and not another developmental condition. As a means of expanding their research, the researchers discovered that autistic people with those specific gene variants associated with autism were more intelligent and quick-witted than individuals on the spectrum who do not have these variants. Likewise, the gene variants were in the cerebral cortex, which is the part of your brain that is responsible for complex behaviors. Ultimately, these variants play a huge role in how brain neurons function and connect with one another. Similarly, the gene variants also play a role in gene regulation, turning other genes on or off. A certain pathway that is triggered or inhibited by these variants could result in the development of autism (Drake).

The Environment

Additionally, many scientists believe that chemicals from the environment interact with the central nervous system which ultimately causes autism. To start, it has been proven that

heavy metals, such as lead, cadmium, arsenic, and mercury, have been linked to ASD. Not to mention, pesticides and insecticides are another cause of autism. According to the published study titled, "Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children: population based case-control study," pesticide exposure was linked with autism spectrum disorder, suggesting the fact that specific pesticides were able to alter gene expression and have neurobehavioral effects (Ehrenstein). Finally, exposure to neurotoxicants at a young age has also been associated with the development of autism.

Moreover, according to Saringer, "early exposure to an unpredictable environment and too much exposure to screen time in the developmental years may cause autism."

Biological Factors

According to Miller, research has proven that several problems regarding "brain connectivity, growth or overgrowth in certain areas of the brain, and metabolism (how the body produces energy)" have been linked to the development of autism.

In addition, there has been some research that connects problems in the body's immune system, which protects against infections, with autism. These problems include the functionality of the immune system, inflammation, and the creation of antibodies to a condition that the body isn't used to. As said earlier, infections during the pregnancy process "could increase the child's likelihood of having autism," (Miller).

Additionally, scientists have recently discovered a connection between autism and mitochondrial function (Miller). Mitochondria creates most of the energy for the cell, generating ATP through oxidative phosphorylation. As stated by Miller, "Scientists suggest that mitochondria are also affected by some of the same environmental factors that can increase the chances of someone being diagnosed with autism."

Neurological Factors

According to Drake, current research suggests a connection between certain types of cell malfunctions and autism. At the Lieber Institute for Brain Development in Baltimore, MD, a group of scientists noticed "a decrease in the integrity of myelin, a protective sheath surrounding nerve cells in the brain, in mice with a syndromic form of autism" (Drake). As a result, the results of their investigation showed that there was a "gene variant-based malfunction" in certain cells that produce myelin called oligodendrocytes. In their study, which was published in *Nature Neuroscience*, they determined that this malfunction could result in limited myelin production in the nerve cells and possibly disrupt communication between nerves in the brain. With mouse models, more investigations are happening that consist of treatments that could increase the myelination in the brain in order to see whether it improves the behaviors that individuals with autism struggle with (Drake).

The Gut Microbiome

Another considerable factor that researchers are taking into account is the gastrointestinal (gut) microbiome. According to Drake, multiple studies have shown a connection between autism and imbalances in the gut biome. In addition, several studies have proved that stabilizing the populations of gut microbes can work towards improving some of the disadvantageous behaviors that autistic individuals have. One particular study published in the journal Microbiome in 2017 focussed on Microbiota Transfer Therapy (MTT) in autistic children. After the MTT treatment, not only was there a decrease in gastrointestinal symptoms, but the individuals also experienced more gut bacterial diversity, and displayed improved language, social interaction, and behavioral symptoms. In a follow-up investigation, researchers found that those who received the MTT treatment had fewer gastrointestinal issues and ultimately continued to show improvement in symptoms related to autism. Furthermore, in a recent study, researchers discovered that mice that lack a gene related to autism called CNTNAP2 have a population of microbes in their intestines and show "some social behaviors similar to those seen in some autistic people." After the mice were treated with a common strain of gut bacteria that is found in wild-type mice and a common bacterium missing from the microbiome called *Lactobacillus reuteri*, the social behaviors of the mice improved drastically. Ultimately, this study suggests a link between the gut microbiome and genes (Drake).

Other Factors

Furthermore, it is proven that older parents are more likely to have children with autism. Additionally, having an immediate family member who has autism increases the risk of developing it. Another risk factor for autism is if "the frontal cortex of the baby's brain overgrows shortly after birth" (Miller).

According to Autism Speaks, boys are four times more likely than girls to have autism. As stated by Morrison, "It takes fewer variants to predispose a boy to developing autism than it does a girl. That is, girls may be spared autism even though they have the same number and kinds of genetic variants that cause the condition in boys."

The health of the mother is another factor that is being considered when it comes to the causes of autism. According to Saringer, "the odds of an autism diagnosis increase nearly 50% if the mother has been diagnosed with a mental health condition." In addition, vitamin D deficiency in the mother has been linked to autism spectrum disorder, as well as the intake of folic acid. Likewise, according to Cherney and Seladi-Schulman, some other risk factors for ASD include "low birth weight, metabolic imbalances, a maternal history of viral infections, and fetal exposure to the medications valproic acid or thalidomide."

Lastly, Miller indicates that it is more likely for a child to be diagnosed with autism if during pregnancy the mother had hypertension or diabetes, experienced an antepartum hemorrhage in the third trimester or postpartum hemorrhage, or had preeclampsia. According to Sarris, "Several studies found that pregnant women with diabetes – including the temporary kind – had a higher risk of delivering a child with autism than mothers who weren't diabetic."

Additionally, hemorrhage during pregnancy is heavy bleeding, and several sources, including NCBI, indicate that hemorrhage is a factor that causes autism. According to marchofdimes.org, preeclampsia causes high blood pressure and causes organs to malfunction. As stated by NCBI, "Preeclampsia can increase risk for developing autistic disorders."

Vaccines

One important thing to note is that vaccines have been proven to not cause autism. In 1998, in the British medical journal, called Lancet, a study stated that not only do measles and mumps cause autism, but the rubella (MMR) vaccine causes autism as well. Eventually, the study was proven to be false and was retracted (Miller).

How Autism is Currently Diagnosed

Specific screenings and evaluations are used to diagnose autism. According to Miller, clinicians who are diagnosing ASD generally look for "difficulty with back-and-forth conversation, differences in nonverbal communication like facial expressions or body language, and difficulty adjusting behavior to different social settings."

Additionally, developmental screening for autism consists of various questions that determine whether the child has autism by comparing their behavior to other children of the same age (Cleveland Clinic). One development questionnaire, mentioned by Cherney and Seladi-Schulman, is called Autism Diagnostic Observation Schedule, Second Edition (ADOS-2). When screening for autism, a doctor may look at specific behavioral patterns including specific movements, obsessive interests, attachment to routine, and differences in sensory processing (Miller). It's important to note that screenings don't always identify autism in a child. According to Cherney and Seladi-Schulman, "The American Academy of Pediatrics (AAP) recommends that all children undergo ASD screening at ages 18 and 24 months," because they help to identify ASD in children at a young age. A common screening tool is called The Modified Checklist for Autism in Toddlers (M-CHAT), which consists of a 23-question survey (Cherney and Seladi-Schulman).

Other tests that may be used to identify autism in an individual include DNA testing for genetic diseases, visual and audio tests to rule out any issues with vision and hearing that aren't related to ASD, and occupational therapy screening (Cherney and Seladi-Schulman).

In addition, another test that is helpful for diagnosing autism is a neuropsychological evaluation, which looks at the history of the child's behavior, in addition to "cognitive and achievement testing, as well as further specialized testing of memory, attention, and executive function, to pinpoint a child's abilities and deficits in learning and communicating" (NYULangone).

Lastly, a formal evaluation for autism takes an in-depth look at the child's behavior and "gives them a structured autism spectrum test" (Cleveland Clinic). Ultimately, these evaluations determine specific strengths and challenges for the person, which is, in essence, a formal diagnosis.

New Diagnostics

To start, according to Baumer and Frueh Health, the FDA approved a new tool that helps to diagnose autism in children. The evaluation consists of a questionnaire answered by the parents, short videos of the child eating and/or playing, and lastly, a questionnaire answered by the medical providers. As described by Baumer and Frueh, "an algorithm compiles the information gathered from those three sections and provides a result of either 'ASD,' 'no ASD,' or 'indeterminate.'"

In addition, "the U.S. Food and Drug Administration (FDA) has granted 'breakthrough device' designation to a hair-based test designed to aid autism diagnosis," according to Dattaro. The hair-based test is called StrandDx. In essence, by examining a strand of a child's hair, the test is able to determine the levels of chemicals in the strand, which captures "a snapshot of [their] 'exposome' — some of [their] cumulative environmental exposures and how [they] regulate certain essential nutrients" (Dattaro).

Moreover, the FDA has also approved an app from Cognoa which diagnoses ASD by examining videos of kids communicating with others and doing tasks in addition to analyzing reports from doctors and caregivers (Park).

Another fascinating app that Cognoa has created uses AI to diagnose autism in children and FDA has cleared it. According to Park, "the EarliPoint Evaluation uses eye-tracking technology to monitor a child's focus and responsiveness while viewing short videos of social interactions between other kids." In essence, artificial intelligence is able to study the eye movements of the child and draw conclusions from the results by comparing them to reference points based on the child's age. As a result, if AI observes any substantial differences, it concludes that the child's social, verbal, and even non-verbal abilities aren't close to the standard for their age, which suggests that they have autism (Park).

Furthermore, another test for ASD uses blood and urine to determine autism. Many are skeptical about it, however, according to Enzo, it "could lead to earlier diagnosis and intervention and potentially identify new causes of ASD." Essentially, researchers took blood and urine samples from fasting children and were able to test for markers of oxidation, nitration, and protein glycation. As stated by Enzo, "Modified protein damaged by metabolic processes including oxidation and glycation were evaluated and used to predict ASD… Changes in the plasma AGEs likely suggest dysfunctional metabolism and reduced renal clearance that could enable high sensitivity detection and diagnosis specificity for ASD." Researchers at the University of Warwick executed practically the same experiment. They found a link between damage to proteins in the blood's plasma and autism. Their most accurate blood and urine test concluded that children on the spectrum had higher levels of dityrosine and advanced glycation end-products (AGEs) (Sandoiu). According to Sandoiu, "Dityrosine is a marker of oxidation damage, and AGEs are the result of glycation," a process where sugars combine with amino acids. Ultimately, this test was 92% accurate.

Conclusion

Essentially, there are several different factors, including genetic, environmental, biological, neurological, and more, that result in the development of autism. Not only are the combination of various factors that cause autism interesting but also the fact that there is a spectrum and every autistic individual is different from one another is super fascinating. In essence, every single child with autism is unique and special in their own way. Therefore, autism is completely different from other disabilities due to the fact that it is a spectrum disorder. Ultimately, autism affects people in completely different ways. Autistic individuals vary in their abilities, strengths, and challenges, which ultimately sets autism apart from any other developmental disorder. The Centers for Disease Control and Prevention (CDC) states that the rate of autism diagnosis is higher than ever before (Ries). Ultimately, this accentuates the fact that we must grow awareness of ASD so that it can start to be diagnosed in children early on in order for them to get the support they need right away. In conclusion, the beauty of autism is that people on the spectrum are authentic and entirely themselves. Dr. Temple Grandin, a professor with autism, once said, “I am different, not less.” I believe our world can learn a lot from this quote.

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The Use of Machine Learning in Gut Microbiome Studies: Implications for Health and Disease By Ryan A. Chien

Abstract

Artificial Intelligence (AI) has been a rapidly growing field that shows promise in revolutionizing medicine. Its branch of machine learning (ML) in recent years, with access to large clinical data sets from electronic health records, has demonstrated efficacy with its increases in computing power and big data processing abilities. By being able to deal with large and complex data found in medicine, ML may be the future for biomedical research, personalized medicine and the advancement of global health care.

The human gut is host to an immense community of microorganisms called the microbiome. It has been a focus of increasing research in recent years and has been shown to play a crucial role in human health. Numerous diseases, from gastrointestinal dysfunctions to neurological deficits, have been linked to the gut microbiome and various therapeutic interventions have been studied.

Omics-based methods are commonly used to study the gut microbiome because they produce high-throughput and high-resolution data. Most of the data generated by these methods has led to the advancement of computational methods for data processing and analysis, with ML becoming widely used in this field. ML methods have generated promising results for disease prediction however challenges are still present. Small sample sizes, inconsistent experimental protocols, or a lack of access to pertinent metadata can all lead to a lack of reproducibility and efficacy when predicting illnesses.

Here we review the subjects of ML, gut microbiome and its significance in relation to disease, current ML methods used in microbiome research, challenges with these processes and future outlook.

Machine Learning

Machine learning (ML) is a branch of computer science and artificial intelligence (AI) which uses data and algorithms to mimic the way that humans learn. The term “machine learning” was coined by Arthur Samuel with his research involving the game of checkers. A checkers master, Robert Nealey, played the game in 1962 and lost to the computer.

The essence of ML is to present algorithms that utilize input data, administer computer analysis to predict output values, identify patterns and trends within the data and then learn from past experience. The computer is given the data and it produces analytical models based on a learning structure to refine and improve the predictive accuracy. One simple example of an ML process is training a computer to detect cancer from histopathological slides. One could attempt to program the computer by using a knowledge base of features that have been shown to represent the presence of an invasive disease. With ML, a database of malignant and non-malignant images could be presented to the computer and then allow it to determine the best way to differentiate between the two categories. (Handelman et al 2018)

Within AI and ML, there are two approaches which are supervised and unsupervised learning. In supervised learning, the computer is equipped with features related to the learning objective (such as risk factors and patient demographics) and desired outcome measures to be attained (such as clinical events or diagnoses) with the goal of finding links between those two in the data set. Examples of supervised learning algorithms include linear regression, decision trees, and support vector machines. In unsupervised learning, the computer is given unclassified data to recognize and determine whether any existing underlying patterns are present. Unsupervised learning can help identify patterns in data that may not be obvious. Algorithm examples include clustering, dimensionality reduction, and anomaly detection (Mesko et al 2020).

ML has grown in recent years in the technology sector as well as in medicine. The ability to analyze large data sets and predictive models enables clinicians to diagnose, predict and treat patients with more confidence. This in turn allows for a greater recognition of variables within a patient, and this individualization leads to personalized medicine in diagnosis (Dilsizian et al 2014), prognosis and treatment (Cruz et al 2007, Menden et al 2013). In 2007 on PubMed, there were a total of 370 articles published on "machine learning" and in 2017, there were 3978 articles published. (Handelman et al 2018)

Gut Microbiome

The gut consists of a community of trillions of microorganisms which include bacteria, archaea, viruses, fungi, protozoa and helminths, all of which exist in a symbiotic relationship with the human host. Their collective genome contains 100 times the number of genes in the human genome (Almeida et al 2021, Li et al 2014). In recent years, there has been a considerable increase in research on these gut organisms, referred to as microbiota, due to the developing knowledge of the significant role that they play in human health. The development of high-throughput sequencing and population-level analysis of the human gut microbiome from the Human Microbiome Project (HMP 2012), Belgian Flemish Gut Flora Project (Falony et al 2016) and METAgenomics of the Human Intestinal Tract (MetaHIT) Project (Qin et al 2010) have all increased our knowledge of host–microbiome interplay and suggest that medical interventions with the gut microbiome could be performed. Various diseases have been linked with a disruption (dysbiosis) of the balanced relationship between the gut microbiota and gut epithelial cells, including liver diseases (Chu et al 2019), inflammatory bowel disease (Lloyd-Price et al 2019), colorectal cancer (Yu et al 2017), diabetes (Vatenen et al 2018), cardiovascular diseases, obesity (Ley et al 2006), and neurological disorders (Cryan et al 2020),(Kazemian et al 2020). Growing evidence exists that altering the gut microbiota could be a potential approach to prevent or treat diseases such as through dietary changes (Ghosh et al 2020), supplementation with probiotics (Le Barz et al 2015), prebiotics (Rastall et al 2015) or fecal microbiota transplantation (Camarota et al 2014).

Machine Learning Gut Microbiome Studies

The term "omics" is derived from the word genomics, which initially focused on the study of genes and their functions. “Omics” fields have expanded and omics-based methods involve high-throughput technologies, data analysis, and integration to generate extensive datasets that provide a systems-level understanding of biological processes and diseases. Methods such as metagenomics, metabolomics and metatranscriptomics are widely used to assess the human gut microbiota. For example, metagenomics techniques (e.g.,16S rRNA gene sequencing or whole-genome shotgun sequencing) provide data regarding the overall genetic content of the microbial community of interest, and metabolomics measure the concentrations of various compounds generated by that particular community (Aguiar et al 2016). These omics-based methods have generated large amounts of data, which have lead to the development of computational methods, such as machine learning, to assist in processing and analyzing this data such as in human gut microbiota research (Ghannam et al 2021). (Fig. 1).

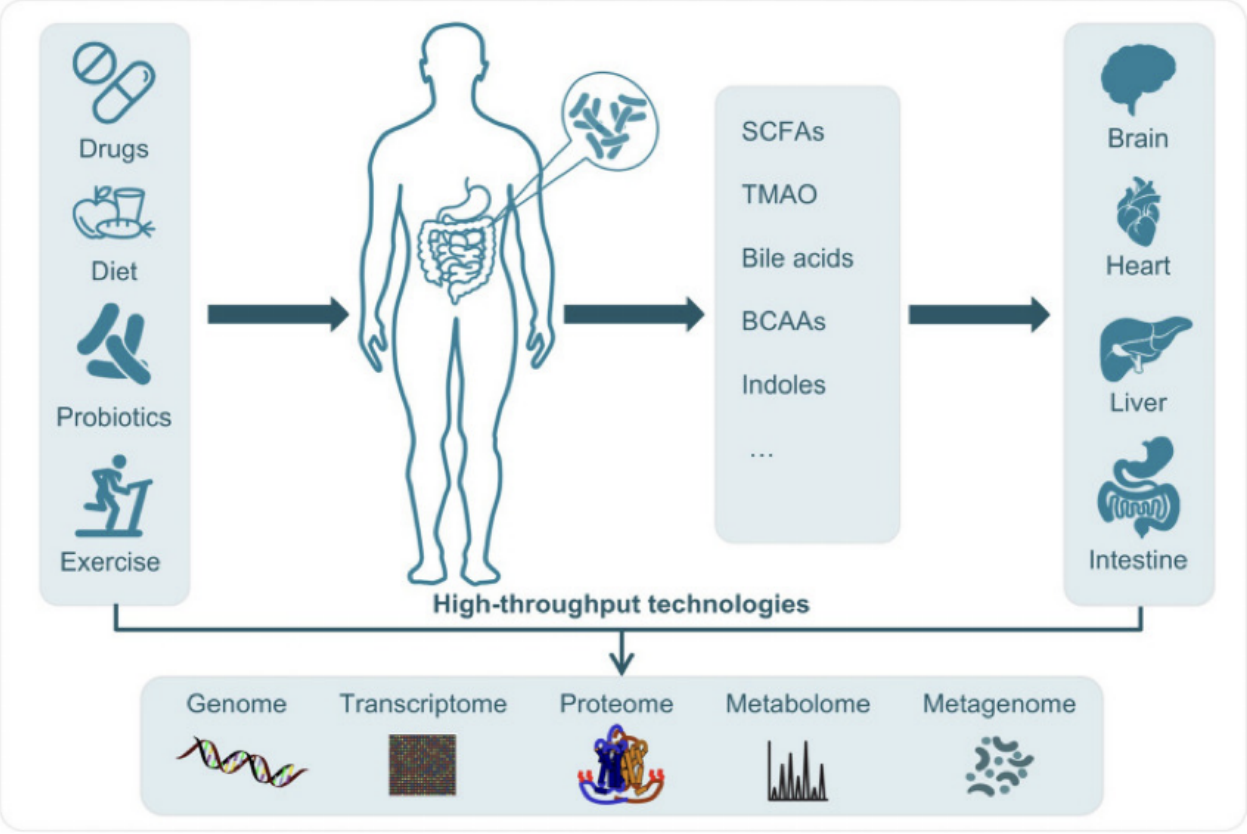

Fig 1. Li et al. “Machine learning for data integration in human gut microbiome.” Microbial Cell Factories 2022.

Machine learning (ML) has great potential to incorporate multi-omics data for identifying hidden patterns and for creating models that can accurately predict phenotypes (Lawson et al

2021, Lin et al 2017). Also, biomarkers linked to human diseases could be identified through interpretable models (Carrieri et al 2021), thus enabling us to attain novel insights into diseases and identify potential therapeutic strategies. Also, a growing number of studies have employed deep learning, a subcategory of machine learning that uses multiple layers of processing to extract progressively higher degrees of data, to analyze the gut microbiome (Oh et al 2020). ML techniques have been applied in a number of studies to analyze human microbiome data, studying the diverse microbial communities and their impacts on human health.

There have been studies on classification models (Vervier et al 2016), host phenotypes in disease prediction (LaPierre et al 2019), and the use of microbial communities to stratify patients (Yachida 2019).

There are a large number of ML algorithms currently in use for medical research, some of the more common in the literature being SVM, NN, Deep learning, decision tree learning, and latent variable models. (Handelman et al 2018)

Computation methods are vital to discovering potential microbiological patterns to improve disease diagnosis or predict therapeutic responses. For example, based on gut microbiome composition, (Zeller et al 2014) developed a logistic regression model to differentiate colorectal cancer (CRC) patients from healthy subjects. Peptostreptococcus stomatis and Fusobacterium nucleatum were identified as the most relevant species to the prediction model. (Derosa et al. 2020) found that some species (Clostridiales hathewayi and Clostridiales clostridioforme) were associated with drug resistance and metastasis in patients undergoing immunotherapy for renal cell cancer. In a study in the New England Journal of Medicine showing that computational technique design is not confined to data analysis, (Chen et al 2021), conducted a randomized controlled trial to determine the effect of a microbiota-directed complementary food intervention to treat undernourished children by using an analysis base on linear mixed-effects models, resulting in weight gain and restoration of “healthy” microbiota composition to a significant degree.

Challenges

Applying ML to these studies is not without challenges. One is the dependence of supervised learning models on both the quality and quantity of training data. This can lead to non-reproducible models due to small sample sizes, inconsistent experimental protocols, or a lack of access to relevant data (Schloss 2018).

Also, heterogeneous data with large amounts of features (genes, species, metabolites, etc.) but relatively small sample size makes it difficult to develop accurate prediction models. Deep learning includes many parameters and requires large amounts of data for training. In addition, it has been difficult to integrate multi-omits data and determine interactions that contribute to disease. Many factors, such as drugs, age, diet, could confound associations between the gut microbiota and a unique disease which make it difficult to build ML models with high accuracy. Another limitation of ML is in conducting multi-site trials that usually generate datasets with different samples and inconsistent variables. (Li et al 2022)

Certain methods may require a specific type of input data format, making the preprocessed data incompatible. Many researchers feel the expansion of public repositories providing more human gut microbiome-omits data is an important step which could lead to a greater usage of machine learning techniques. (Giuffre et al 2023)

Sequencing costs, sample collection challenges and patient recruitment limit the number of available samples that will be available for a given study. Microbial communities also exhibit fluctuations especially with illness. Since the most informative sample collection time has not yet been established, this dynamic environment raises concern. (Curry et al 2021)

Future

With many unexplored protein sequences, ML may be further used to predict protein structure for drug or enzyme development. Based on gut microbiome and diet information, ML can be applied to design diet or therapeutics for certain patients. ML can also be used to assist in design of probiotics. (Li et al 2022)

Conclusion

Computational techniques, especially machine learning, have played a vital role in analyzing the large volume of data produced by multi-omics studies of the human gut microbiota. This in turn has led to the discovery of new associations between microbes and disease (Ghannam et al 2021). The use of machine learning processes relies heavily, however, on data availability and requires expertise to ensure reproducibility and accuracy. Recent developments in data repositories (Dai et al 2021), reporting guidelines (Mirzayi et al 2021), and frameworks (Wirbel et al 2021) have fortunately improved the accessibility and efficiency of the data analysis process. These advancements have enabled a shift from observational association to causal inference studies and clinical intervention (Wilkinson et al 2021).

Based on this information as well as the success of AI accompanied by big data, machine learning appears to be well-suited for analysis of gut microbiome. These approaches will be crucial in advancing our understanding of the complex relationships between the human gut microbiome and disease and can be helpful for the development of gut microbe-targeted therapeutics, which could ultimately help in achieving personalized/precision medicine. Hopefully this will lead to improved health outcomes for patients.

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IL6 Induced the mRNA Expression of HIF-1α Mediated TG2 in Mouse Lung Fibroblasts

By Akhil Datla, Varun B. Raju, Yamini Sharma, Rod Warburton, Krishna Penumatsa

Abstract

Pulmonary hypertension is a chronic and fatal disease that affects approximately 200,000 people every year in the US alone (Mayo Clinic, 2022). Several research studies have found that pulmonary arterial inflammation leads to the progression of pulmonary hypertension disease. Pulmonary hypertension is shown to be associated with an increase in interleukin 6 (IL6), hypoxia-inducible factor-1α (HIF-1α) and transglutaminase 2 (TG2) levels. However, it remains to be addressed if the upregulation of inflammation-mediated by IL6 is the causing factor for the upregulation of HIF-1α and TG2 levels, or if they function independent of each other. We hypothesized that IL6 treatment will lead to an upregulation of HIF-1α mediated TG2 expression in experimental pulmonary hypertension. The results showed that IL6 treatment significantly increased both HIF-1α and TG2 mRNA levels in mouse lung fibroblasts. Furthermore, we found that IL6 induced TG2 expression, which is mediated by HIF1α. Thus, these results support our hypothesis and lead to the conclusion that inflammation induces upregulation of HIF-1α, which in turn mediates fibrogenic remodeling in experimental PH.

Introduction

In pulmonary hypertension (PH), pulmonary arterial (PA) inflammation leads to PA adventitial fibrogenesis. The resulting PA remodeling is associated with increase in PA resistance, which leads to increased right ventricle pressure and eventually results in heart failure. Ongoing research aims to identify molecular mechanisms and novel drug targets for PH disease which currently has no effective treatment. The pro-inflammatory cytokine interleukin 6 (IL6) is amongst the most important inflammatory cytokines shown to be involved in vascular diseases associated with both systemic hypertension and pulmonary hypertension [1]. Recent studies have implicated fibroblasts in several of the PH pathologic features including inflammation and fibrogenesis that lead to PA tissue remodeling [2]. IL6 is thought to play an important role in PA adventitial remodeling associated with PH [3]. HIF1α up-regulation is a well-known common transcription regulator of PH associated genes, shown to play an important role in PA remodeling and PH disease progression [3]. HIF-1 is a heterodimeric transcriptional factor, which consists of low oxygen-dependent regulation of HIF1α and constitutively expressed HIF1β subunits. Penumatsa et al have recently shown that hypoxia induces HIF1α-mediated TG2 regulation [4]. However, the inflammation-mediated molecular mechanisms involved in TG2 regulation in PH disease progression are unclear. Previous studies report that TG2 is important in PA remodeling, which includes fibroblast cell growth and differentiation, fibrogenesis [4]. Furthermore, it was shown that TG2 activity is highly elevated in lungs of an experimental mouse model of pulmonary hypertension (PH) produced by exposure to hypoxia and that the elevated PH was reduced by TG2 inhibitor, ERW1041E [4]. Thus, it remains to be addressed if the upregulation of inflammation-mediated by IL6 is the causing factor for the upregulation of

HIF-1α- mediated TG2 levels, or if they function independent of each other. We hypothesized that IL6 treatment will lead to an upregulation of HIF-1α mediated TG2 expression in experimental pulmonary hypertension. In my present study, with the cell culture experiments, I wished to determine the inflammation mediated mechanisms in PH and if inflammatory cytokine, IL6 is associated with increase in HIF1α-mediated TG2 levels.

Materials and Methods Reagents

Recombinant human IL6 was purchased from R&D Systems (Minneapolis, MN). HIF1α inhibitor, PX-478 was purchased from Selleckchem Chemicals (Houston, TX). Both the reagents were dissolved in sterile phosphate buffer saline (PBS).

Cell Culture

We used fibroblast cells previously isolated from mouse lungs. Cryopreserved cells were thawed in a water bath which was maintained at a constant 37°C. Then, the cells were gently transferred to sterile tubes with fibroblasts culture media supplemented with 5% fetal bovine serum and fibroblasts growth factors (FGM™-2 Fibroblast Growth Medium-2 BulletKit; Lonza, Cambridge, MA). Cells were then centrifuged and replaced with fresh media to remove the cryopreservation reagent, dimethyl sulfoxide (DMSO; Thermo Fisher Scientific, Waltham, MA). Shortly after, the cells were transferred and cultured in sterile cell culture plates. Confluent adherent fibroblasts were treated with 0.25%trypsin-EDTA (to detach the cells from the plate; Thermo Fisher Scientific) and subcultured into a 6-well cell culture plate. The two 6-well plates were divided into three groups: 1) vehicle control group; 2) cells stimulated with IL6 (10 or 20 nanograms [ng]); and 3) cells pre-treated with HIF1α inhibitor (PX478; 10μM) for 30 minutes and followed by stimulation with IL6 (20 ng).

RNA Isolation and Quantitative RT-PCR

After 24 hours, the RNA was extracted using standard Trizol technique (ThermoFisher Scientific). Total RNA and RNA purity was estimated using a Nanodrop 2000 instrument (ThermoFisher Scientific). A total of 1μg of total RNA from the 6 samples were then treated with DNAse I enzyme, which helps remove any extraneous DNA strands from the RNA sample, before being placed in the thermal cycler for 30 min at 37°C to remove all genomic DNA. The samples were then treated with magnesium chloride at 60°C for 10 minutes to deactivate the DNAse enzyme. Then, complementary strand synthesis was performed using a reverse transcriptase kit, and qPCR analysis was used to determine the relative mRNA expression of HIF-1 and TG2. 18s ribosomal RNA levels were used to normalize the cycle threshold (Ct) values. A ΔΔCt method was used to express the relative quantification of specific genes as previously described [4].

Statistical Analysis

Experiments were independently replicated at least three times. Data was reported as mean±SD. Statistical analysis will be performed by one-way analysis of variance. A p value of <0.05 is considered statistically significant.

Results–IL6 media induces HIF1α and TG2 mRNA Expression in Mouse Lung Fibroblasts.

The qPCR analysis revealed that 10ng of IL6 increased HIF1α and TG2 mRNA expression by 1.3 and 1.2 fold respectively (**Figure 1**). Additionally, we found that 20 ng of IL6 treatment significantly increased the HIF1α and TG2 mRNA expression by 2.2 and 1.5 fold respectively (**Figure 1**). As the IL6 concentration increased, the expression of HIF-1α and TG2 also increased. Additionally, since the error bars did not overlap between the control group and either of the IL6 concentrations for both HIF-1 and TG2, it can be deduced that the results were not deduced from random chance. Thus, our in vitro studies using mouse lung fibroblasts show that IL6 treatment markedly increased HIF1α and TG2 mRNA expression.

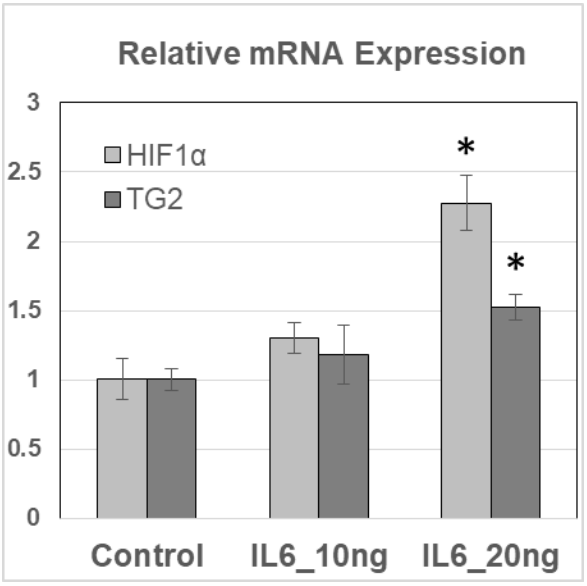

Figure 1. HIF1α and TG2 mRNA expression are increased in response to IL6 stimulation in mouse lung fibroblasts. *Quantitative PCR analysis demonstrates the effect of IL6 (10 and 20 ng) on HIF1α and TG2 mRNA levels in mouse lung fibroblasts. Bar graph demonstrating average fold change in target mRNA expression normalized to 18s ribosomal RNA by ΔΔCT method. Values are mean±SD (n=3 independent replicates/ group). *compared to the control group. p<0.05 is considered statistically significant.*

Inflammation-induced TG2 mRNA expression is mediated by HIF1α activity in mouse lung fibroblasts. Hypoxia has been shown to play a critical role in HIF1α activation and the proliferative phenotype of PA adventitial fibroblasts. Pretreatment with PX-478 (10μM), a specific inhibitor of the HIF1α activity, blocked the IL6 induced TG2 mRNA expression (**Figure**

2). Thus, HIF1α may be one connecting link between enhanced inflammation and TG2 regulation and fibrogenesis.

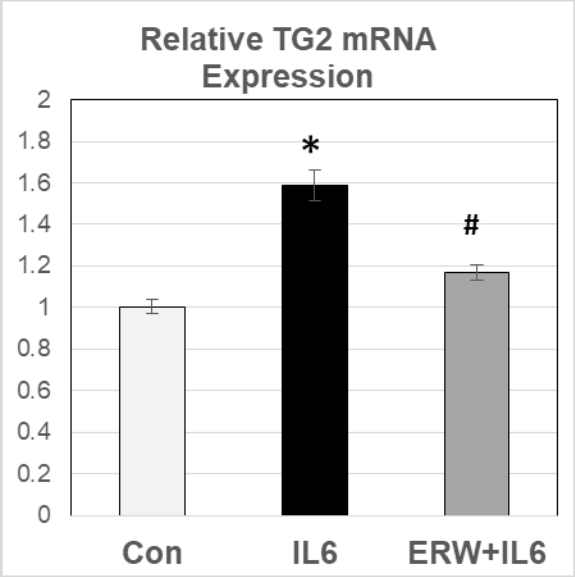

Figure 2. IL6 -induced expression of pro-fibrogenic TG2 was mediated by HIF1α activity in mouse lung fibroblasts. *Quantitative PCR analysis demonstrates the effect of control (phosphate buffered saline) or IL6 (20 ng) ±HIF1α inhibitor, PX-478 (10μM) on TG2 mRNA levels in mouse lung fibroblasts. Bar graph demonstrating average fold change in target mRNA expression normalized to 18s ribosomal RNA by ΔΔCT method. Values are mean±SD (n=3 independent replicates/ group). *compared to the control group. #compared to IL6 stimulation. $p<0.05$ is considered statistically significant.*

Discussion

To summarize our results, we found evidence that inflammation elevates HIF1α and TG2 mRNA expression, which may regulate PA remodeling in PH. Penumatsa et al previously reported that hypoxia stimulates TG2 expression in PA fibroblasts via HIF1α activity [4]. This concept is supported by previous studies of a role for the transcription factor, HIF1α, in pathogenesis of PH [5]. For the first time, our current study shows that inflammation also mediates HIF1α induction and thereby participates in tissue fibrosis by its action on TG2. Targeting up-regulated HIF1α or TG2 expression may lead to a novel therapeutic approach for managing PH.

Conclusion

We have established that IL6 treatment induces HIF-1 and TG2 mRNA upregulation, thereby answering the question of the potential role of IL6 in regulation of HIF-1 and TG2. Our current findings suggest that IL6 is involved in stimulation of TG2 and further support our overall hypothesis that HIF1α plays a key role in inflammation-induced lung remodeling in PH.

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An Analysis of Video Game in Humanity through Bibliometrics and Scientific Mapping By Sherlock Chen

Abstract

The popularity of video games has increased rapidly throughout recent years, primarily among teens but also among adults. This surge in popularity and revenue leads to the question of how video games have impacted and evolved in humanity. So far, no study has explored this question through the use of scientific mapping and bibliometrics. To bridge this gap, this study used Web of Science to gather bibliometrics from peer-reviewed journal articles and analyzed them with VOSviewer. The procedure resulted in the top 30 terms being sorted into 7 clusters (two positive, three negative, and two neutral) by their relation to video games. Moreover, the network visualization presents the pattern and relationship between the 30 terms. The overlay visualization shows the evolution of the 30 terms over three time periods. The density visualization displays the hottest research terms. In other words, this research points out the top terms related to video games, the terms' evolutions, and the most popular terms in video game research. The most important contribution is that future research can build upon this study to develop new research directions.

Introduction

Video games are becoming increasingly prevalent in the lives of humans today. During the COVID-19 pandemic, lots of people were forced to stay at home for extended periods of time and often experienced anxiety, aggression, and cognitive problems. With a 12.7% annual gain in revenue, the video game market in the United States reached revenues of over 85 billion dollars in 2022, up from 61.11 billion dollars in 2020 ("Topic: Video Gaming in the United States"). In addition, the global video games market site, which was valued at USD 188.73 billion in 2021, is projected to grow to USD 307.19 billion by 2029 (*Video Games Market Size, Growth*). In fact, over 84% of teens in the U.S. have access to a gaming console at home, and 43% of adults in the U.S. play video games in general (Perrin, 2018). Considering the staggering rise in profit and popularity of video games, it is imperative to understand how video games are affecting people. Not fully understanding the impact of video games can lead to costly misinterpretations about them, such as using video games to improve mental/physical health when they actually worsen it. However, if the effects of video games are thoroughly researched, it can enable humans to maximize their positive usages, such as recognizing that video games improve mental/physical health and making full use of them to help people.

Many previous studies have been done to analyze the effects of video games and the factors influencing them, such as family environment (e.g., Geniş and Ayaz-Alkaya, 2023), video game content (e.g., Garcia et al., 2022), and individual motivation (e.g., Garakani et al., 2021). Some studies show beneficial impacts of video games, such as improved cognitive skills (e.g., Smirni et al., 2021), educational enhancements (e.g., Toh and Lim, 2022), and social development (e.g., Bailey et al., 2006). Moreover, there are still other studies that point out the

drawbacks of video games, such as sedentary issues (e.g., Harding and Noorbhai, 2021), social isolation (e.g., Eren, 2018), and increased aggressive behaviors (e.g., Chen et al., 2022). The methods of these studies include self-report surveys (e.g., Harding and Noorbhai, 2021), observations (e.g., Toh and Lim, 2022), literature reviews (e.g., Smirni et al., 2021), and experiments (e.g., Chen et al., 2022).

Humanity is defined as the study of human values, beliefs, experiences, and practices. The relationship between video games and humanity has already been studied. Some examples in the area of video games include policy making such as game content restrictions (Király et al., 2017), healthcare usages such as physical rehabilitation through virtual reality (VR) (Ali et al., 2023), and education purposes such as personalized gamified learning (Smiderle et al., 2020). These integrations are important because understanding their uses will allow humanity to promote meaningful experiences via video games while also addressing the concerns society has about them through the examples provided previously. For example, Pallavicini et al. (2022) adopted systematic reviews and followed meta-analysis guidelines to find that playing video games reduced stress, anxiety, depression, and loneliness during the COVID-19 pandemic. Despite the surplus of studies, none has yet focused on an integrated and synthesized overview of the evolution of video games about humanity through bibliometrics and scientific mapping.

There has been no research using bibliometrics and scientific mapping in studies relating to video games. Bibliometrics is a method for analyzing large volumes of data through patterns and trends (Donthu et al., 2021). Similarly, scientific mapping is a technique used to visually model a broad range of data and knowledge (C. Chen et al., 2014). Using scientific mapping and bibliometrics in research helps the researcher understand the landscape of the field better, which can help in evaluating research impact as well as identifying research gaps and trends. Therefore, the purpose of the study is to identify the major topics, develop the flow, and contribute to the future research of video games in humanity. To reach the goal, this study collected 210 articles from Web of Science and used VOSviewer to analyze relevant literature. The following methods explain the data source and software used in the study. Results show the terms related to video games, changes over time, and the most common terms in video game research. Contributions, limitations, and future research are discussed in the conclusions.

Methods

Web of Science (WoS) is a scientific search and analytical information platform that is used by researchers to explore academic studies (Li et al., 2017). This website provides the user with comprehensive coverage of tens of millions of bibliographic records as well as billions of citation connections, which can greatly aid researchers in conducting literature searches and managing references. Based on a study by Li (2017), researchers from 125 countries have used WoS in their studies, with the journal Cochrane Database of Systematic Reviews having the most papers (1359 in total) mentioning WoS. Therefore, this study adopted WoS, which provides rich and preferable bibliographic records, to explore video games in humanity.

The information and data for this paper were gathered by using the keyword "video game," including author keyword and keyword plus, a unique function of the WoS system that defines the keyword. The use of keywords can be effective in filtering out irrelevant results and focusing on the specific ones that relate to the topic of study. For example, the keyword "video game" was inputted into WoS and the results were narrowed down to only include peer-reviewed journal articles in English, which counted 729 articles in total. Only articles in peer-reviewed journals were chosen since they provide preferable and comprehensive knowledge based on previous studies, which is helpful for identifying research trends and gaps for potential future research.

Next, each abstract of the 729 articles was reviewed one by one based on video games and the relevant topics about humanity, such as cognitive behavior, personality traits, and mentality, excluding neurology, photosensitivity, or therapy. The final data set for analysis resulted in 210 articles from 141 journals in total. The major journals were *Journal of Behavioral Addictions* which had nine in total, *Computers in Human Behavior* which had seven in total, and *Games for Health Journal* which had six in total. While most journals (e.g., *Aggression and Violent Behavior*) provide only one article, the three journals provide research reports on addictive patterns of various behaviors (*Journal of Behavioral Addictions*), examinations of computers from a psychological perspective (*Computers in Human Behavior),* and research about the impact of games on human well-being (*Games for Health Journal*) in the humanities area.

VOSviewer is a computer program used to construct and view bibliometric maps (Van Eck and Waltman, 2009). This software is widely used among researchers because of its ability to create large bibliometric maps through graphical elements, such as sizes, colors, distances, and clusters, to make them easy to interpret. VOSviewer has already been used in many areas of studies, such as social and behavioral sciences (Flis and Van Eck, 2018) and medicine research (Zhao et al., 2018).

As for this paper, VOSviewer was used to import the bibliographies of the 210 articles from Web of Science. Keywords were aligned, such as "Videogame" to "video game" and "internet gaming disorder" to "igd." The function of full counting was the import process used, where all occurrences of a term (e.g., video game and igd) in a document were counted. Full counting means that a publication is fully assigned to each term, as opposed to fractional counting, where the credit is split among all the terms (Waltman and Van Eck, 2015). Full counting treats each term equally and makes interpreting citations more straightforward. For example, if video games and igd occur in two articles, each has two counts. The minimum number of occurrences of a term was then set to 16, which resulted in 102 out of 5069 items meeting the threshold. The main purpose of setting the number of occurrences to 16 is to get about 100 items. The 102 items were evaluated, and the top 30 most important items were selected to analyze. Table 1 shows the 30 items in 7 clusters, each with 2-6 items. Each item was assigned to one cluster based on the closeness between them (Van Eck and Waltman, 2009). In other words, the items in the same cluster are highly correlated to one another.

Results

Table 1 contains seven clusters: the first cluster focuses on anxiety and stress; the second, learning and training; the third, aggression; the fourth, physical engagement; the fifth, psychiatric disorder; the sixth, mental health; the seventh, cognitions. The clusters may cover psychology or psychiatry. However, all represent the high-level functions of brain perception, thinking, behavior, and emotion. Three clusters are negative and specific (anxiety and stress, aggression, psychiatric disorder), two are neutral and broad (mental health, cognitions), and two are positive (learning and training, physical engagement).

Table 1 The top 30 items in 7 clusters

Cluster 1 (6 items) Focusing on anxiety and stress	Anxiety Benefit Exergame Inclusion criterium Stress Video game
Cluster 2 (6 items) Focusing on learning and training	Digital game Effectiveness Learning Rehabilitation Serious game Training
Cluster 3 (5 items) Focusing on aggression	Aggression Aggressive behavior Behavior Effect Health
Cluster 4 (5 items) Focusing on physical engagement	Active video game Engagement Esport Impact Physical activity
Cluster 5 (3 items) Focusing on psychiatric disorder	Factor Igd (internet gaming disorder) Treatment
Cluster 6 (3 items) Focusing on mental health	Gamification Mental health Technology

Cluster 7 (2 items) Focusing on cognitions	Attention Cognitive function

Based on the relationships between the clusters, the network visualization created by VOSviewer is made up of circles/nodes and lines/connections to present the comprehensive relationships between each item and cluster. Each node is labeled with an item related to the research on video games in humanity, which totaled to 30 nodes. The larger a node is, the higher the weight of the item is. An item with more weight has more importance than one with less weight. The colors of the items are chosen based on which clusters they are part of (Table 1). The connections show the links between the items, and the distances between the items show how related they are to one another (the further away they are, the less related they are).

In Figure 1, video game and effect are the larger items on this map, showing how they are the two items that had the most impact. The item video game (identified as red in the network visualization) leads the negative terms, such as anxiety and stress, though benefit is most closely related to video game. The effect item(identified as blue) leads another negative cluster, such as aggression and aggressive behavior. However, health and behavior are more important (bigger nodes) than aggression and aggressive behavior. The third negative cluster of psychiatric disorder is located between the terms of effect and igd. Thus, the three negative clusters are close together on the right side of Figure 1. While the positive cluster of learning and training seems to be further away from video game, located on the left side of Figure 1, the cluster of physical engagement is between the negative clusters and the positive cluster of learning and training. The two neutral clusters (mental health, cognitions) are close to the positive cluster of learning and training.

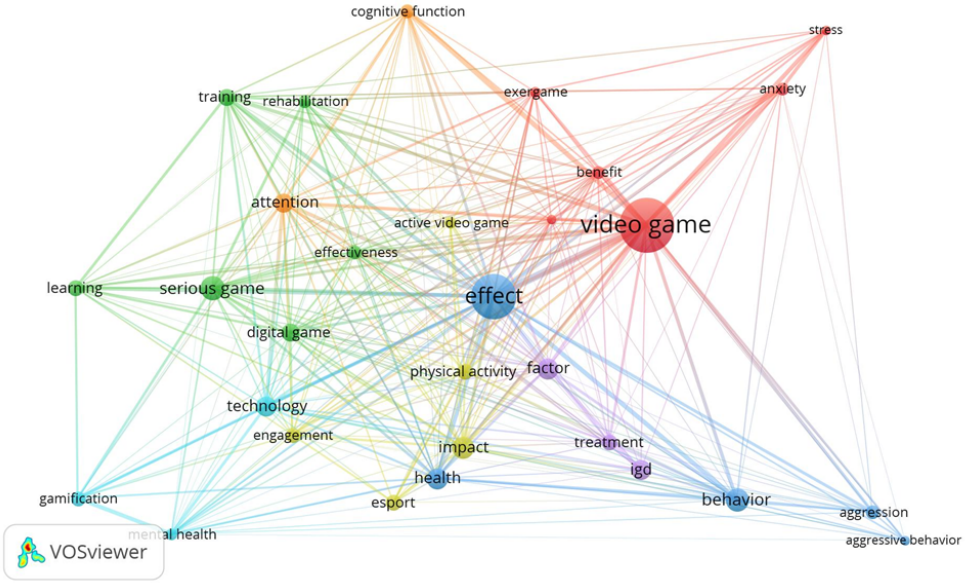

Figure 1 Network visualization of video game

Another type of graph in VOSviewer is overlay visualization, which is like network visualization except that it uses different colors to show the evolution over a span of time. The color bar on the bottom right indicates that items with colors closer to blue are topics that were majorly discussed longer ago (closer to the year 2017), and items with colors closer to yellow are topics that were majorly discussed more recently (closer to 2020). All other elements besides the color are the same for this graph.

According to the figure, there are three main periods for video game research. Around 2017, the research of video games began with video game, effect, benefit, impact etc., which explored the effects or impacts of video games. Between 2018 and 2019, research extended to other types of video games, such as serious game, digital game, etc. Then, the topics also began to include other various topics such as aggression, training, etc., which include a mix of negative and positive terms related to video games. Around 2019, more and more topics focus on negative terms, such as stress, anxiety, igd, while few positive terms are mentioned, such as learning and gamification. These more recent topics tended to be on the edge of Figure 2, while the topics around 2017 were in the center of the graph.

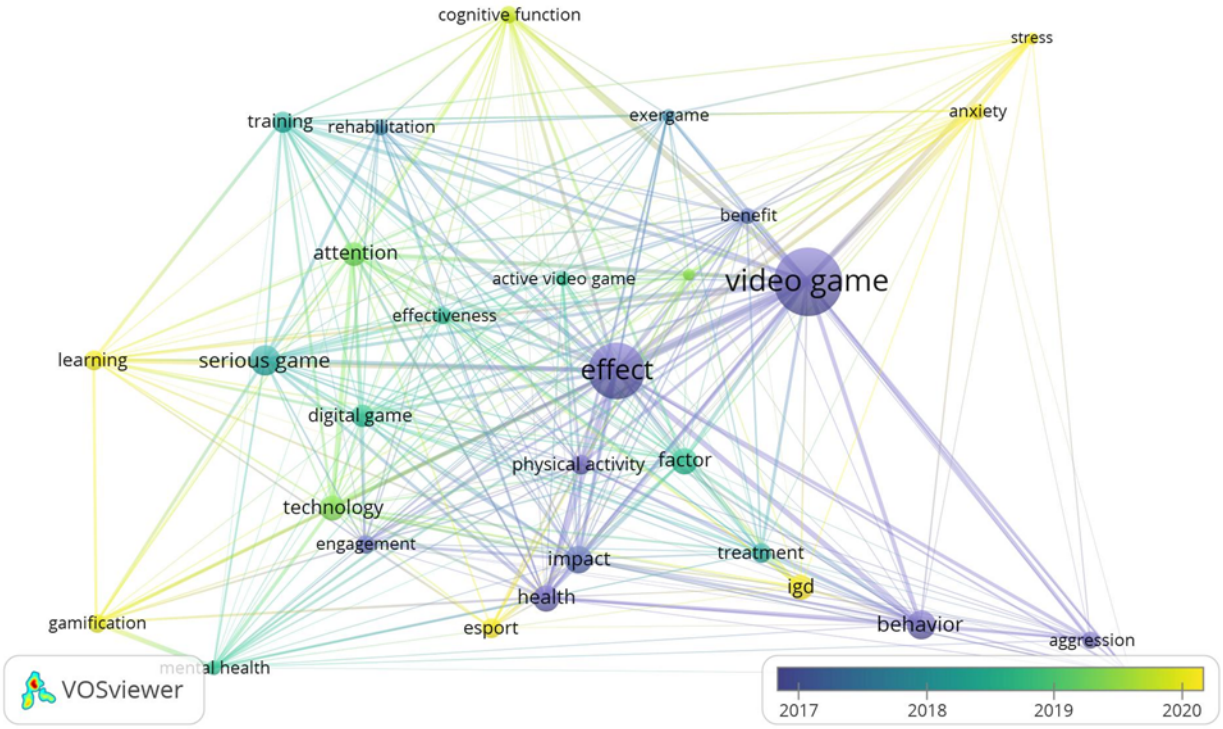

Figure 2 Overlay visualization of video game

The last type of graph from VOSviewer implemented in this paper is the density visualization. The items are laid out in the exact same places as the network visualization and have hues of green, blue, and yellow that are like the overlay visualization. The higher the

weight of an item is, the closer its color is to yellow. Conversely, the lower the weight of an item is, the closer its color is toward blue.

In this density visualization (Figure 3), video game and effect have the highest weight since they are mainly yellow. Other items such as treatment, igd, behavior, impact, health, serious game, and technology have a tinge of yellow, meaning that they still have some weight but not as much. All other items on the map are shades of green, either closer to blue (e.g., exergame, stress, and active video game) or closer to yellow (e.g., aggression, learning, and training), meaning that they are valued at lower weights compared to the mainly yellow items.

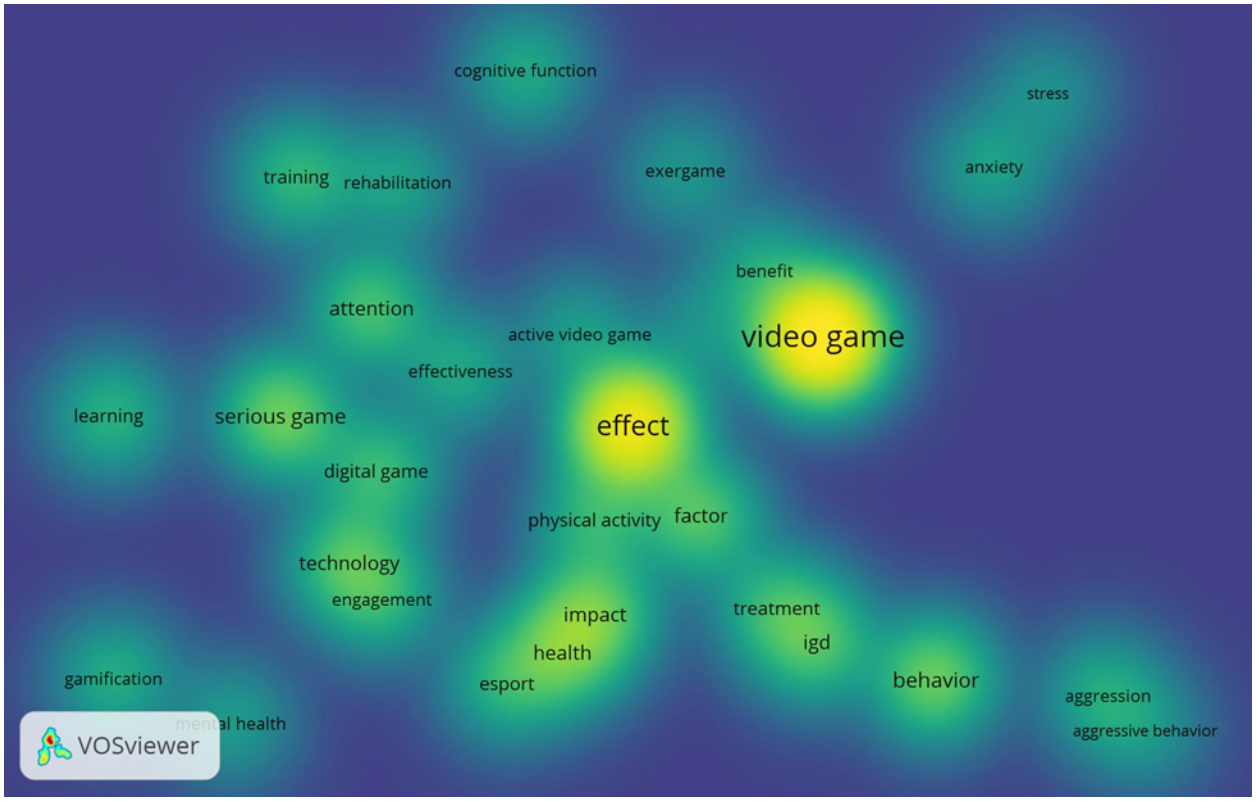

Figure 3 Density visualization of video game

Discussion

Based on the nature of the top 30 terms, this study classified the 7 clusters into three categories (negative, neutral, and positive clusters) to discuss their relationships with video games. In the negative category, anxiety and stress are related to the use of video games because a person may play video games to relieve anxiety and stress (temporary escape from real life problems). On the other hand, a person may also develop anxiety and stress from playing video games (fearing real life responsibilities). Likewise, a person may play certain video game genres (prosocial video games may make people more inclined to help others) to reduce their hostility, while others may develop aggressive behaviors from playing other video game genres (violent video games may encourage aggressive thoughts and behaviors). Various psychiatric disorders apply to this pattern as well, such as addiction to video games, depression, or social isolation. In

other words, either a person plays video games to cope with a problem or problems are caused by a person playing video games. Based on these relationships, future research can explore how video games affect different individuals (e.g., envy, doubt, low self-esteem), how various genres of video games affect these disorders differently (e.g., prosocial and violent video game genres), and how to control these impacts (e.g., limited video game exposure or change of video game content).

The neutral clusters of mental health and cognition also correlate with video games. For example, mental health can be improved for certain people playing video games (playing multiplayer video games to connect with others), or it could deteriorate other people's mental health (social isolation and gaming addiction). Similarly, a person may play video games to improve their cognition (playing strategy video games to improve focus and decision-making) while others may have their cognitive skills hindered by playing video games (impulsive behavior and short attention spans from playing fast-paced action games). These may lead to future research on which aspects already present in some video games, such as problem-solving, multi-tasking, and teamwork, can be incorporated into future video games to benefit humans.

The last category includes the positive clusters of learning and training, and physical engagement. Learning and training can have an impact on a person playing video games based on the content (educational video game genre), where the user learns skills and knowledge in the form of games. Similarly, some genres of video games, such as exergames or VR games, can involve players in physical engagement (having the player move around or do physical motions to play the game). These ideas may lead to future research on the effectiveness of utilizing educational video games in school, work or personality settings, and the use of exergames or VR games as a form of exercise.

Based on Figure 1, the positive and negative clusters are positioned on opposite sides. The negative clusters are most likely closer to the item video game because they can be applied to most video games in general, not just particular niches of video games. For example, stress, anxiety, and behavior can all be reasons why a person plays any kind of video game or how video games affect the person that plays them. The positive clusters are further away from the item video game because while they can be applied to most video games in general, they are most related to specific types of video games. For example, training and learning relate more directly to serious video games than to any video game in general. Lastly, the neutral clusters are spread out in the middle but more towards the positive clusters because they can be applied to most video games in general but can also be more specifically applied to certain types of video games. In other words, the aspects of cognitive function and attention affecting a human player can be found in most video games but can also be more specifically related to the active video game genre. These findings can lead to more categorized research on the implications of video games for humanity in either specific or general video games.

In Figure 2, three periods show the trend of video games. In 2017, the research was to explore the effects of video games, such as what the benefits and impacts were. Between 2018 and 2019, there had already been much research done on the effects of video games on people in

general, so research shifted towards specific types of video games and how they impacted certain people, such as the implications of serious games, active video games, and digital games for humanity. During the COVID-19 pandemic in 2020, many people were under lockdown, meaning that more and more people were playing video games. With less time to go outside and more time to play video games, the problem of excessive gaming became more prevalent, which induced more research to be done on the negative aspects of gaming, such as igd, stress, and anxiety. Video games did help some people cope with being indoors more, so there was still a portion of research done on the positives of video games, such as learning and gamification, in 2020. With the COVID-19 pandemic becoming less prevalent in the future, research may shift back towards the specific applications of video games (similar to the research done in 2018 and 2019), such as rehabilitation and treatment.

Figure 3 shows the importance of terms with different colors. Video game and effect are the most important ones. The reason may be that video games and their effects in general cover all the other items that have less weight. The items with less weight can mostly be sorted into the categories of either video game or effect. For example, serious video games are a more specific type of video game, and they have an effect on the learning and training of their human users. As long as there are broad categories of video game and effect, all the other items can be covered. This is the reason that they have more weight compared to others. There are also items that have less weight than video game and effect but still have more weight than others. For example, behavior has more weight than aggression because aggression can be categorized into a type of behavior, so if there is behavior, aggression is covered as well. This understanding can lead to future research categorizing video games and effects in general, subcategories of those items such as behavior and serious game, and then further narrowed down to more specific subjects such as aggression and learning.

Limitations and Future Research

There are still some limitations to this research, such as the lack of enough samples of articles and software for analysis. The articles from peer-reviewed journals gathered for this research were collected from WoS, which provides various journal articles. However, as only one database was used, some journal articles critical to this study may have been missed. Therefore, future research may include other databases, such as Google Scholar and Scopus, to help create a more comprehensive dataset.

VOSviewer is the only software used to analyze the journal articles collected from WoS. Using only one software to analyze the data means producing a single result, whereas using different software (e.g., SciMAT and CiteSpace) may provide another view of the same dataset. For example, SciMAT can customize different time frames to analyze the collected data and bibliometrics. With the utilization of different software and datasets, future researchers will be exposed to a multitude of perspectives to aid their studies and result in more comprehensive conclusions. This research shows the terms related to video games, terms' evolutions, and the

most popular terms in video game research. The most important contribution is that future research can be built upon this study to develop new research directions.

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Quantification of NAD Pool of Anerobic Archaeon *Methanococcus maripaludis* By Yiqiao Wang

Abstract

In recent decades, the consumption of fossil fuels has led to the imbalanced release of greenhouse gases such as CO_2 into the atmosphere, increasing global temperature. Biofuels and bioplastics could effectively reduce CO_2 emissions to the atmosphere. A cost-efficient approach to synthesizing large quantities of biofuel and bioplastic may be developed through the utilization of *Methanococcus maripaludis'*, a methane-producing archaeon, metabolic pathways. However, the low concentrations of NAD cofactors limit its ability to produce biofuels and bioplastics through transformed pathways. To further understand *M. maripaludis'* NAD pool, its relationship with *E. coli's*, an LDH-based NAD assay was used to quantify the NAD concentration of *M. maripaludis* and *E. coli*. This study successfully justified the existence of NAD cofactors within *M. maripaludis* and calculated the NAD pool to be approximately 29% the size of *E. coli's*. While the specific size of *M. maripaludis'* NAD pool remains unclear, this study hinted at the potential of enhancing it through possibly overexpressing genes within its NAD biosynthetic pathway, allowing it to better express transformed glycolytic metabolic pathways.

Introduction

The consumption of fossil fuels has led to the release of greenhouse gases, drastically impacting Earth's climate by increasing atmospheric temperature (Environmental Protection Agency). According to the Intergovernmental Panel on Climate Change (IPCC), to prevent an additional temperature increase of over 1.5°C, the release of carbon dioxide (CO_2) which accounts for 79% of human-related emissions in 2020 (Environmental Protection Agency), must not exceed the carbon budget of 420-570 gigatons (Gt). The two main sources of CO_2 emission are transportation and industry, which account for 33% and 27% of total CO_2 emissions respectively (Environmental Protection Agency). Besides the combustion of fossil fuels, which contributes to a fixed share of emissions within these sources, the synthesis and disposal of plastics have become a prevalent issue. Plastic's share of CO_2 emissions is expected to take up to 10-13% of the total carbon budget by 2050 (Hamilton and Feit 19).

Biofuels and bioplastics could effectively decrease CO_2 accumulation in the atmosphere. However, most methods of biofuel and bioplastic production remain within the developmental phase, as it is difficult to produce large quantities at a relatively low cost. Through the utilization of *Methanococcus maripaludis'* metabolic pathway, it may be possible to develop a novel, cost-efficient approach to synthesizing large quantities of biofuel and bioplastic.

Methanococcus maripaludis is a methane-producing archaeon that inhabits the anaerobic sediments of a South Carolina salt marsh (Ladapo and Whitman 1). It possesses a relatively simple genome and the fastest measured doubling time among methanogens of 2 hours, making it a logical target for cultivation and transformation (Goyal et al. 1). *M. maripaludis* generates energy through methanogenesis, a metabolic process that reduces simple carbon substrates (such

as CO_2 and formate) into methane while generating ATP using the H^+ concentration gradient generated by HS-COM methyltransferase (Goyal et al. 2-5).

M. maripaludis is capable of surviving within nutrient-deficient environments by effectively distributing energy to maintain methanogenesis capacity (Müller et al. 2-5). *M. maripaludis* possesses the energy-efficient Wolfe cycle, which is capable of synthesizing acetyl coenzyme A (a precursor to molecules of biofuels or bioplastics) from the widely available substrates CO_2 and H_2 (Thauer 1).

Furthermore, *M. maripaludis* has stable protein contents across environments with varying nutrient levels (Müller et al. 3). This could ensure stable expression of transformed genes even under environments with relatively low nutrient levels. Thus, the utilization of *M. maripaludis'* metabolic pathway to produce biofuel and bioplastic precursors may be a cost-effective and future-friendly approach that could further the aim of decreasing additional CO_2 emission in the carbon cycle. Methane produced through methanogenesis by *M. maripaludis'* metabolic process could be a valuable, harvestable byproduct that can be utilized while producing biofuels or bioplastics through a transformed pathway (Thevasundaram et al. 1).

A challenge in successfully producing biofuels and bioplastics in *M. maripaludis* is its lack of the redox cofactor NAD. While it has a native NAD synthesis pathway, it has relatively low NAD+ and NADH concentrations that are approximately 12% of *E. coli's* (Thevasundaram et al. 3). This is insufficient to sustain biofuel or bioplastic synthesis pathways engineered with genes from organisms with glycolytic metabolisms. While mainly dependent on low-potential redox coenzymes such as F_{420} and ferredoxins for its metabolic pathway, *M. maripaludis'* capability of synthesizing NAD+ through its biosynthesis pathway makes it possible to enlarge its NAD pool through overexpressing genes of its NAD+ biosynthesis pathway.

A previous study conducted by Thevasundaram et al. successfully overexpressed each of the genes within the NAD synthesis pathway individually (Figure 1) to expand the NAD pool from approximately 100nM/mg dry cell weight (DCW) to more than 500nM/mg DCW. They then introduced NAD into *M. maripaludis'* growth environment and were able to enhance the synthesis of the bioplastic PHB and its monomer by two orders of magnitude (Thevasundaram et al. 4-5). Thevasundaram et al. showed a positive correlation between *M. maripaludis'* NAD concentration and its production of bioplastics, making it a valuable candidate for further genetic transformation.

The measurement of NAD+/NADH concentrations by Thevasundaram et al. was described in terms of nM/mg DCW. While nM is a concentration, mg DCW is not, meaning it may be challenging to interpret and compare Thevasundaram et al.'s results with further research as no volume of the sample solution was provided. To further understand *M. maripaludis'* NAD pool, its relationship with *E. coli's*, and to express such relationship with relatable units, this project aims to re-quantify the NAD concentration of *M. maripaludis* and *E. coli* through a leucine dehydrogenase (LDH) based NAD assay and contrast the total NAD concentrations of *M. maripaludis* and *E. coli*.

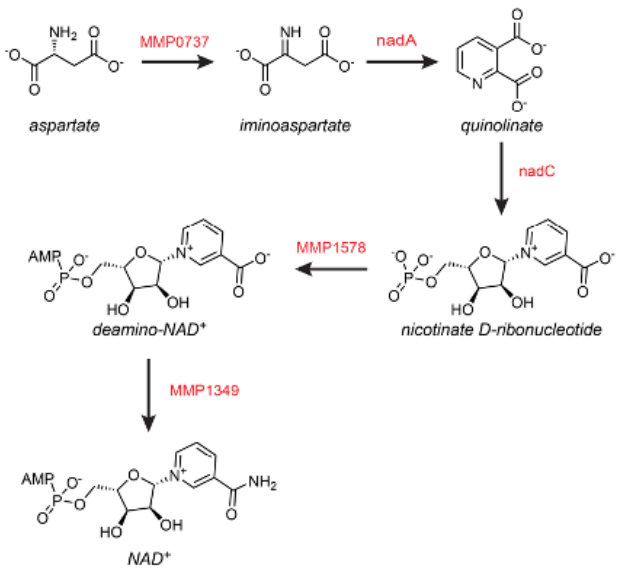

Figure 1: Biosynthetic pathway of NAD+ of *M. maripaludis* showing key enzymic processes that leads to the synthesis of NAD+ (Thevasundaram et al., 2022).

Methods–Cell Cultivation

A stock of *E. coli* competent cells was inoculated in M9 minimal media agar using sterile techniques and grown at 37 °C for 48 hours. Two 10mL M9 liquid cultures were then created and inoculated with colonies from M9 agar and grown at 37 °C with slight shaking at 60rpm. OD at 600nm was monitored daily until the values reached 0.4-0.6.
6g of wet *M. maripaludis* cells were obtained from Professor Whitman at Georgia State University and were frozen at -80 °C.

Cell Collection

E. coli cells were harvested by multiple rounds of centrifugation at 13300 G for 5 minutes. Supernatants were then replaced by more cell culture in between rounds of centrifuging. All supernatants were then carefully removed, and the cell pellet was frozen at -80 °C.

Dry Cell Weight Calculation

The DCW of *E. coli* was calculated by leaving the centrifuge tube with the pellet under the fume hood for 30 minutes for the remaining supernatants to dry off. Then, the mass of the tube was measured.

***E. coli* and *M. maripaludis* Cell Lysis**

Both *E. coli* and *M. maripaludis* were lysed in 1% lysozyme buffer consisting of 50 mM pH 8 Tris HCl, 5% glycol, and 25 mM NaCl. 1mL of buffer was used for *E. coli* while 5mL was used for *M. maripaludis*. Both samples were incubated at 37 °C for 2.5 hours, moved to an 80°C digital dry bath (Bio-Rad) for 15 minutes, and then frozen at -80 °C. Before adding lysozyme to

NAD Concentration Measurements

NAD was quantified using an LDH-based NAD assay (Figure 3) modified based on the Yang et al. (2002) using 300 µL 0.2 M pH 10.8 KCl-KOH-glycine buffer, 10 µL 100 mM l-leucine, 10 µL 0.5-unit LDH, and 10 µL lysis product. Absorbance was measured at 340nm for the three samples within each sample group (Figure 2) using an SQ-2802 Single Beam Spectrophotometer (Unico). Controls for the effects of l-leucine, LDH, and cell lysis were created.

A standard curve was created based on performing the NAD assay on known NAD+ concentrations of 3mM, 30uM, and 300nM.

NAD concentrations of all samples were calculated based on the standard curve and normalized to mg of DCW.

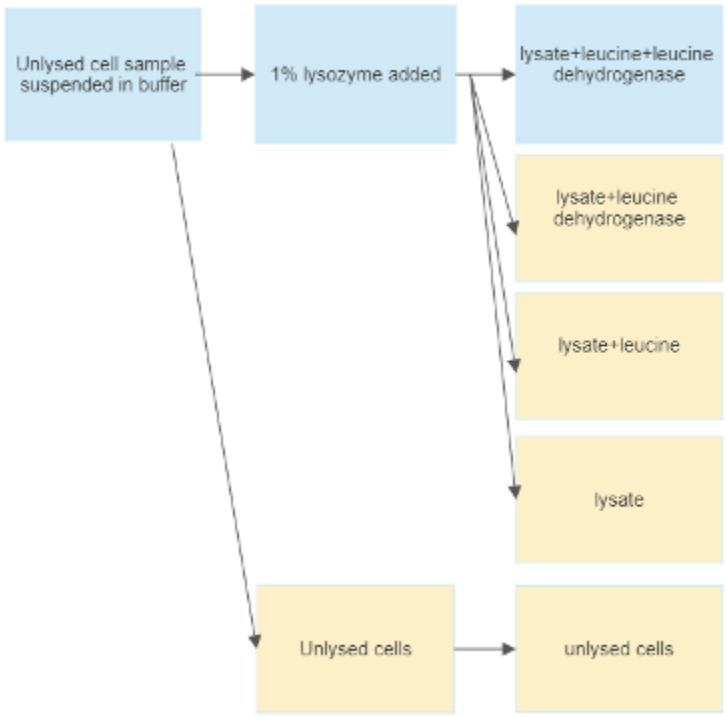

Figure 2: Flow chart of cell lysis and NAD assay. Blue boxes refer to the experimental process while yellow boxes highlight control sample groups. An LDH-NAD assay was performed on all control and experimental sample groups.

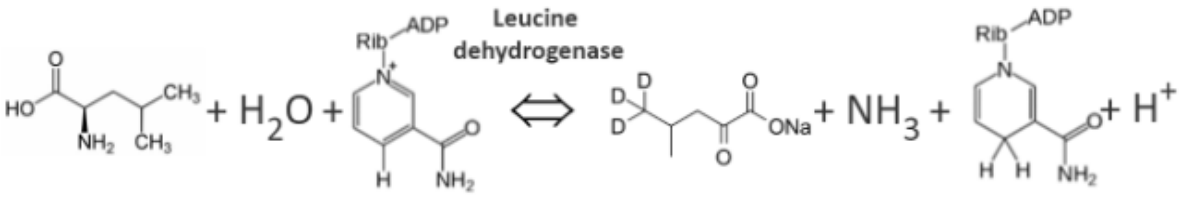

Figure 3: Reduction of NAD+ into NADH through reacting with l-leucine and LDH.

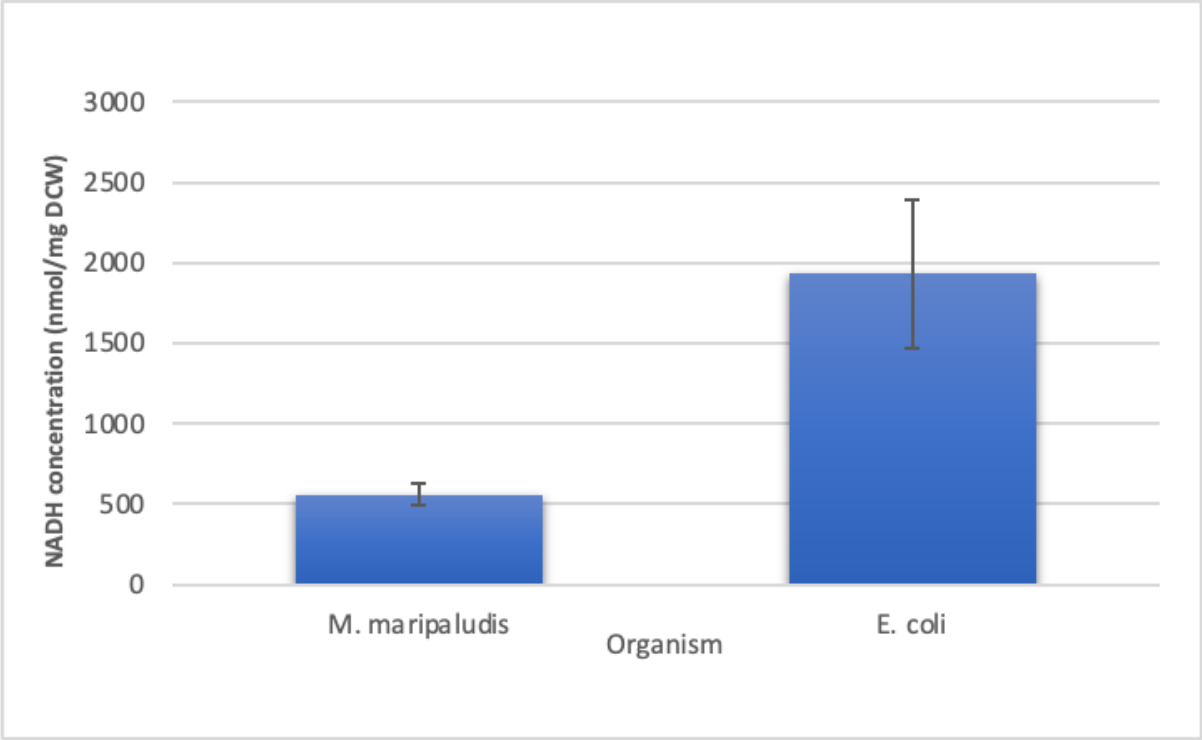

Figure 4: NAD concentration for each organism normalized to mg DCW. Error bars represent standard deviation. The NAD pool of *M. maripaludis* is approximately 558±67 nmol/mg DCW, while that of *E. coli* is 1931±463 nmol/mg DCW.

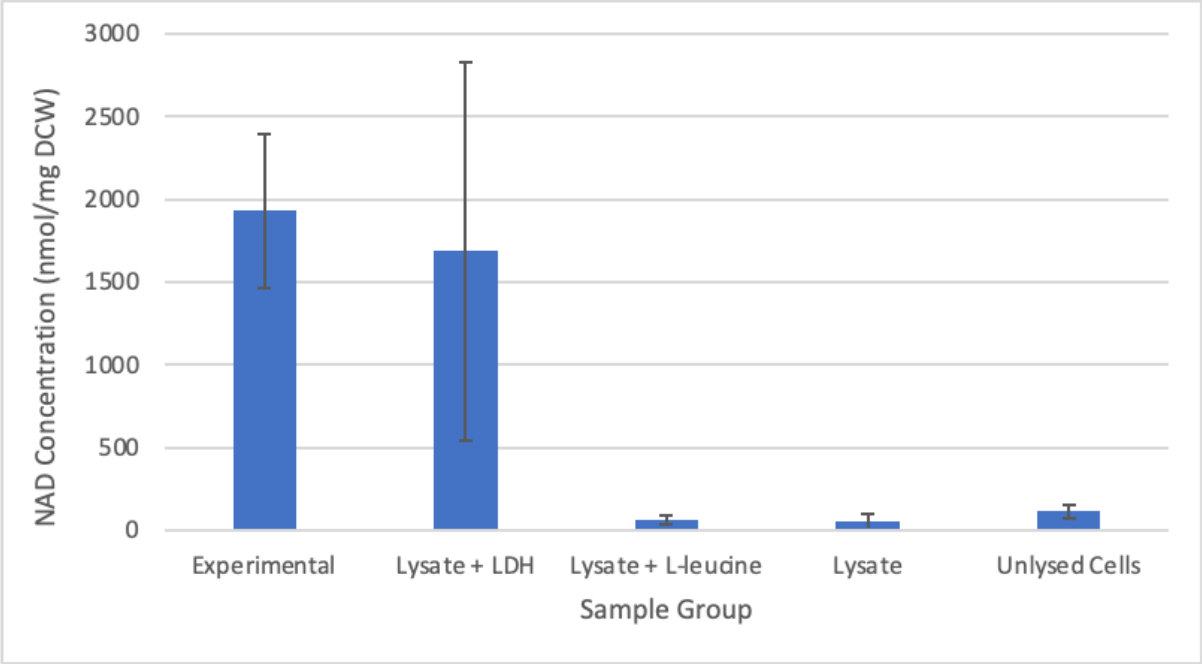

Figure 5: Average NAD concentration of three trials of each *E. coli* sample group is displayed. Error bars represent standard deviation. The experimental sample and the sample of lysate +

LDH had the highest NAD concentration; NAD concentration of the three remaining samples was statistically similar.

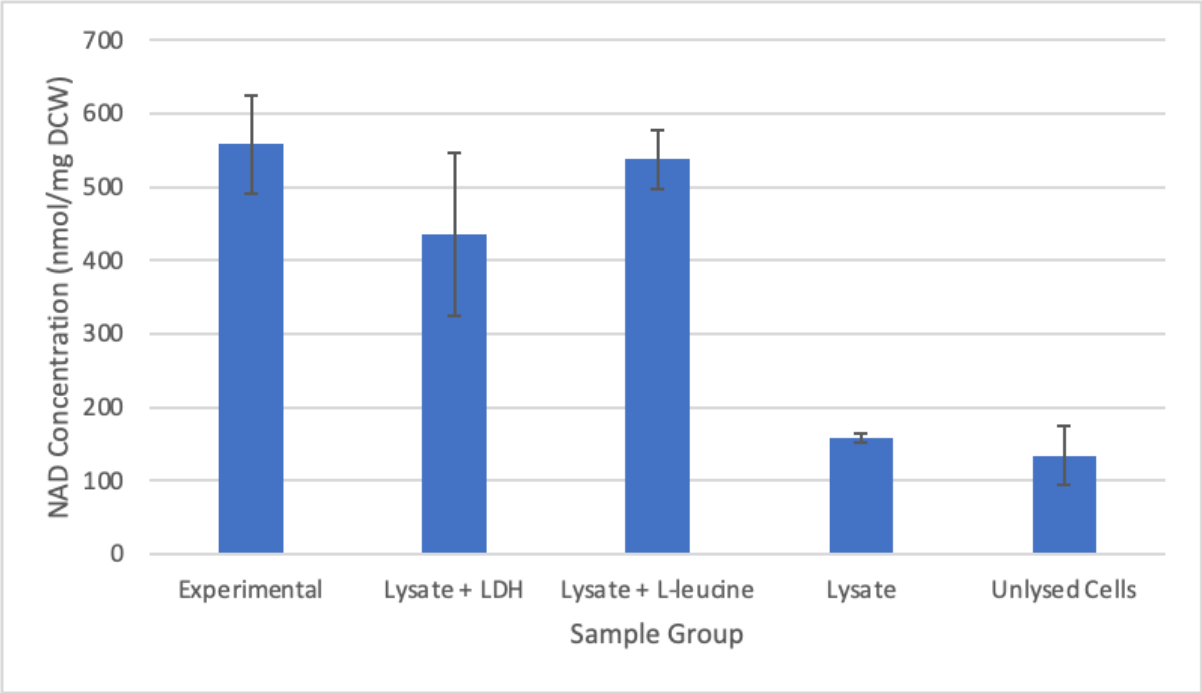

Figure 6: Average NAD concentration of three trials of *M. maripaludis* sample group. Error bars represent standard deviation. The experimental sample, the sample with lysate + LDH, and the sample with lysate + l-leucine had the highest NAD concentration; NAD concentration of the two remaining samples was statistically similar.

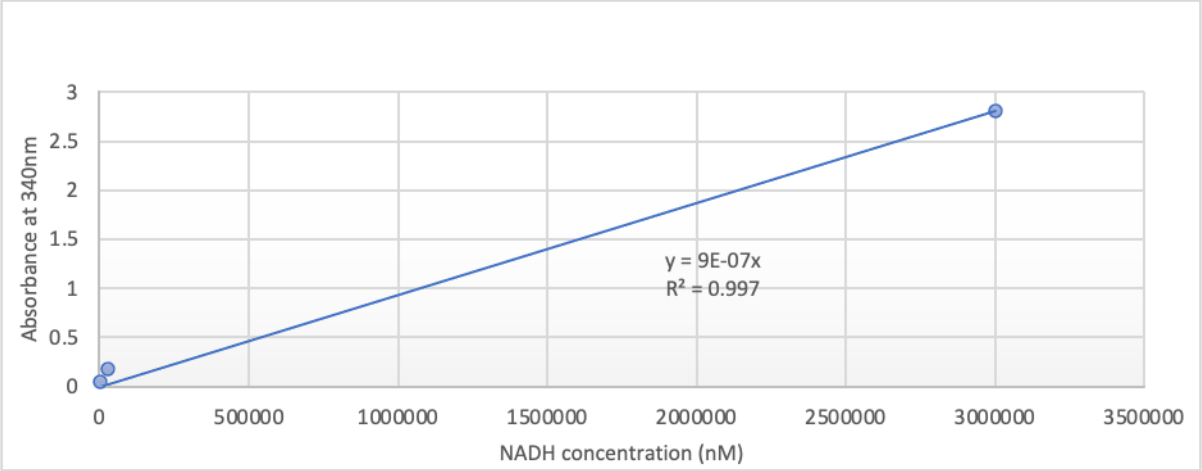

Figure 7: NAD assay standard curve based on three known NAD+ concentrations: 3mM, 30uM, and 300nM. The line of best fit was used to estimate the NAD concentration experimental samples.

Conclusion

Like the findings of Thevasundaram et al., this study successfully demonstrated the existence of NAD cofactors within *M. maripaludis* while showing deficiency compared to *E. coli* with relatable units. Although *M. maripaludis'* NAD pool was quantified as approximately 29% rather than 13% of *E. coli's*, the results of this project supported its claim that *M. maripaludis'* small NAD pool may be the rate-limiting factor of its production of bioplastics and biofuels.

Further research can determine the possibilities of overexpressing multiple genes within *M. maripaludis'* NAD+ synthesis pathway, expanding its potential for the expression of biofuel and bioplastic synthesis pathways.

Discussion

This project successfully quantified the NAD+/NADH concentration within *M. maripaludis* and *E. coli* and showed that the size of *M. maripaludis'* NAD pool is approximately 29% that of *E. coli's* (Figure 4).

The difference in NAD concentration between the experimental sample and the lysate + l-leucine sample of *E. coli* illustrated LDH's successful reduction of NAD+ into NADH (Figure 5). The similar concentration of the experimental sample and the sample with lysate + LDH is likely due to the innate presence of l-leucine within *E. coli* cells (Wang et al. 1). As a key precursor to secondary metabolites within most bacteria, l-leucine can be catabolized into sources of carbon and nitrogen within the central metabolism under nutrient-deficient environments. Since the *E. coli* used in this project are cultivated in M9 minimal liquid media, it is natural for *E. coli* to maintain a storage of l-leucine that will be released when lysed and catabolized by LDH during the NAD assay.

The similarity between the NAD concentration of the experimental sample and the lysate + l-leucine sample of *M. maripaludis* may be a result of the innate presence of enzymes that catabolized l-leucine and reduces NAD+ (Figure 5). It is known that *M. maripaludis* is capable of catabolizing amino acids, including l-leucine, utilizing them as a carbon source under low-nutrient environments (Whitman et al. 2-4). According to Díaz-Pérez et al. cellular l-leucine could be catabolized by the branched-chain amino acid aminotransferase (BCAT) into α-ketoisocaproic acid, and then into glutamic acid. Glutamic acid may then be catabolized by enzymes such as glutamate dehydrogenase (GDH), which also reduces NAD+ into NAD (Díaz-Pérez et al. 3), increasing measured NAD concentration. According to *M. maripaludis'* genome sequence in the Kyoto Encyclopedia of Genes and Genomes (KEGG), both BCAT and GHD exist within *M. maripaludis'* genome. Such enzymes would likely react with the added l-leucine, reducing NAD+ into NAD(KEGG).

The similarity between the NAD concentration of the experimental sample and the lysate + LDH sample of *M. maripaludis* may be due to LDH catabolizing amino acids beyond l-leucine (Figure 5). Beyond catabolizing l-leucine, LDH is also capable of the oxidative deamination of l-isoleucine, and l-valine while reducing NAD+ into NADH (Yamaguchi et al. 357). According to KEGG, it was found that *M. maripaludis* possesses both an l-valine and l-isoleucine

biosynthetic pathway from pyruvate or Acetyl-CoA, meaning the similar measured NAD concentration as the experiment sample may be the result of the introduced LDH reducing all cellular NAD+ while catabolizing the cellular l-leucine, l-valine, and l-isoleucine.

The similarity between the measured NAD concentration of the lysate sample and unlysed cells sample for both *E. coli* and *M. maripaludis* (Figure 5 and 6) is likely due to the storage of unlysed cell samples under -80°C, which may have broken the cell membranes, leading to the release of cellular NAD contents.

Due to material constraints during the measurement of absorbance at 340nm for the NAD assay, 1mL plastic cuvettes were used instead of quartz. While plastic cuvettes can interfere with absorbance in the UV light range by absorbing parts of the UV that inflate readings (Cuvet.Co), all samples and the NAD standard curve was constructed using measurements from plastic cuvettes. It was assumed that plastic cuvettes would have an equal effect on all samples and NADH solutions. If so, then calculations of NAD concentrations based on the standard curve should be accurate. However, comparing the quantified *E. coli* NAD pool concentration of 1340±463 nmol/mg DCW (Figure 4) with the 5nmol/mg DCW obtained by Sanchez et al., measurements of this project seem inflated (Sanchez et al. 4), indicating the need to investigate the impact of plastic cuvettes on the absorbance at 340nm for solutions with various concentrations.

Furthermore, as the linear standard curve was only based on the absorbances of three 100-fold dilutions of NADH solutions, the points were too far apart to reflect whether their relationship is linear or logarithmic (Figure 7). To resolve this issue, 10-fold dilutions should be used in future experiments to better reflect the relationship between absorbance and NADH concentration.

In the comparison of NAD concentration within *M. maripaludis* and *E. coli*, the cellular NAD concentration was normalized according to mg of DCW, based on the assumption that the lysis rate of cells from both organisms was identical. Performing the same lysis procedure of adding 1% lysis buffer coupled with multiple rounds of freezing under -80 °C to both cell samples could theoretically disrupt the cell membrane/wall of both gram-negative bacteria and gram-positive archaea. However, it cannot be guaranteed that lysis rates are the same since *M. maripaludis* and *E. coli* possesses different cell membrane structures. To increase the validity of comparisons of the NAD concentration of *M. maripaludis* and *E. coli*, lysis efficiency should be evaluated through methods such as measuring OD at 600nm after differential centrifugation or cell-counting after staining with Trypan Blue (Apajalahti et al.).

Overall, the results of the NAD assay validated the existence of NAD cofactors within *M. maripaludis*. While differing slightly from Thevasundaram et al.'s (2022) quantification of 13% of E. coli's NAD pool, this project's results nonetheless demonstrated *M. maripaludis'* relative deficiency NAD cofactors compared to *E. coli* and provided a rough estimation of its NAD pool with relatable units. This project expanded knowledge regarding NAD cofactors within *M. maripaludis*. As *M. maripaludis'* small NAD pool may be the rate-limiting factor behind expressing transformed bioplastic/biofuel synthesis pathways of glycogenic organisms

(Thevasundaram et al. 6-7), this project also pointed out the potential behind the overexpression of multiple genes within its NAD+ biosynthetic pathway to boost biofuel and bioplastic production.

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The Impact of Proton Irradiation on Radish Growth and Germination By Claire Dvorak, Bee Ben Khallouq, and Omar Zeidan

Abstract

Mars has captivated human imagination and prompted ambitious plans for human exploration and settlement. As part of preparing for long-duration missions to Mars, understanding the impact of space radiation on crop growth during flight and while on Mars becomes crucial. This study investigates the effects of proton irradiation on radish seeds, a potential crop for Mars settlements. Cherry Belle radish seeds were exposed to varying doses of proton radiation (0 Gy, 0.5 Gy, 10 Gy, and 100 Gy) using a 250 MeV clinical proton therapy system. The germination rate and plant characteristics, such as leaf number, leaf length, plant weight, and radish bulb weight, were measured. Statistical analysis was performed to evaluate potential differences across the dose groups. The germination rate was 78% for control, 92% for 0.5 Gy, 83% for 10 Gy, and 83% for 100 Gy groups ($p = 0.47$). The number of leaves was 4.8, 5.8, 4.8, and 5.5 respectively ($p = NS$). The mean leaf length was 13.1 cm, 10.7 cm, 11.1 cm, and 12.4 cm, respectively ($p = NS$). The mean plant weight was 5.4 g, 4.5 g, 3.3 g, and 5.1 g, respectively ($p = NS$). The mean harvested radish bulb weight was 2.8 g, 2.1 g, 0.3 g, and 1.6 g ($p = NS$). There were some differences among individual group comparisons, suggesting improved germination at the 0.5 Gy level, and reduced plant properties at the 10 Gy and 100 Gy dose levels. Proton irradiation at varying doses did not significantly impact radish seed germination or plant growth characteristics across the four groups, though there were some differences among individual dose levels. There was a suggestion that low doses may have a beneficial effect on germination rates. As humanity aims to establish sustainable colonies on Mars, understanding the effects of space radiation on crop growth is crucial for ensuring food security during long-term space missions.

Introduction

Mars! The distant red planet has long captured the imagination of humanity, beckoning dreamers, explorers and scientists to venture forth and seek out its mysteries. For those who may dare to embark on this audacious mission, the rewards could be nothing short of extraordinary: the chance to uncover new scientific insights, to push the boundaries of human achievement, and to leave an indelible mark on the annals of history. NASA has been actively working on plans to send humans to Mars for decades, with a number of missions and exploratory initiatives already underway. One of the primary driving forces behind these efforts is the Congressional Authorization Act of 2010, which calls for NASA to develop a long-term strategy for human exploration of space, including a focus on sending humans to Mars in the 2030s [1].

There are many compelling reasons to undertake such an endeavor. Establishing a permanent human presence on Mars could lead to significant scientific research and discovery , and spur technological innovation in aerospace engineering, robotics, energy production, sustainable living, and agriculture. It would pave the way for expanding new industries and commerce in

space, and NASA is already supporting this process with its commercial partnership programs [2]. It could also guarantee planetary resilience and redundancy for long term survival of human species, to safeguard against the threat of meteors and other disasters, which could potentially devastate life on Earth. But perhaps most importantly, it would open up the possibility of creating an interplanetary human civilization, with all the cultural, social, and scientific implications that come with such a feat.

But with great exploration comes great danger, and the perils of space travel are many. Among these, perhaps none is more ominous than the constant bombardment of space radiation. Space radiation is a type of radiation that originates from various sources in the cosmos, including our Sun, but also from distant stars, galaxies, and supernovae. About 90% of space radiation is composed of high energy protons, while the remaining 10% is made up primarily of alpha particles, beta particles, photons and other ions [3]. Astronauts on a one way mission to Mars could be exposed to a total radiation dose of ~500 millisieverts, or ~0.5 Gy, which is equivalent to the radiation dose from about 20 to 25 chest X-rays. This is significantly higher than the annual dose limit for radiation workers on Earth, which is set at 50 mSv per year, and is much higher than the average annual radiation exposure of 0.33 millisieverts on Earth [4]. The risks of exposure to space radiation for humans is relatively well understood, including the risk of radiation sickness, cataracts, cancer, and multiple other diseases [5]. What is less well understood is that exposure to space radiation can also pose risks to the food supply for astronauts on long-duration missions. Radiation exposure can damage plant cells and DNA, causing mutations that can reduce crop yields or make them inedible. Radiation can also interfere with the photosynthesis process, which is essential for plant growth and development. In addition to these direct effects on plants, space radiation can also have indirect effects by damaging the seeds or spores used to grow new crops. This could make it difficult to maintain a sustainable food supply over multiple generations of crops. Yet astronauts will need to grow their own food on long-duration missions because it is not feasible to transport all the food they will need for the entire mission from Earth. Food is heavy and takes up a lot of space, which makes it more expensive than seeds to launch into space. Growing food on board the spacecraft can also provide a sense of psychological well-being and help to create a more sustainable and self-sufficient mission. There are also concerns about the degradation of vitamins and other nutrients in packaged or processed foods over time. Freshly grown produce can provide a more reliable source of calories, vitamins and other nutrients, which is especially important for astronauts who may be exposed to additional stressors that could affect their health. There are two potential impacts of space radiation on crops to consider: 1) seed germination, which is the process by which the seed begins to grow after dormancy and develops into a seedling, and which includes absorption of water, swelling, rupture of the coat, and eventually emergence of the root and the shoot; and 2) subsequent plant growth which results in growth to a full plant, including characteristics such as its expected height, weight, color, number of leaves or nutritional yield.

There has been only limited research conducted on the impact of space radiation on

plants and crops, partly due to limited launch opportunities and significant costs associated with performing research on the International Space Station, and partly due to lack of access to proton particle accelerators to simulate the space radiation fluence on Earth. In an attempt to simulate Martian radiation conditions on Earth, researchers at Delft University in The Netherlands created a radiation environment in aluminum frames with a delivered dose ~270 μGy per day [6], which is similar to the dose rate of ~233 μGy per day measured on Mars, and approximately 17x higher compared to Earth [7] . Cobalt-60 γ-photons were used to deliver the radiation. Rye and cress plants were then grown in these environments. The results showed that germination rates under the Martian radiation dose did not differ significantly from those grown under a control non-radiation environment. However, there was a noticeable discoloration and malformation of the plant leaves in the radiated plants that was not present in the non-irradiated plants. Additionally, the weight of the radiated plants was 32% lower for cress and 48% lower for rye. The authors concluded that the biomass loss could be a major concern for future civilization development on Mars. A key distinction between this study and actual space radiation is the particle used to create the radiation. Because photons do not have a charge and may carry less energy than protons, they damage cell DNA differently, so the effect of protons on plant germination and weight may be even greater.

The site of the Chernobyl nuclear accident in Ukraine, which contaminated a large agricultural area with radioactivity, has been used to provide some insights into the response of plants and crops to long term radiation exposure [8]. Depending on the distance from the power plant, there is still a residual elevated radiation environment similar to conditions in space. Soybeans were planted at various distances (and therefore received various radiation exposure levels from the radioactive power plant) and their growth was studied. The crops were harvested after several months, and the plants in the high-radiation zone weighed half as much as their low-radiation counterparts. Correspondingly, the soybean oil production decreased by ~25%. The researchers also determined that the plants experienced changes on the molecular level in order to try to better protect themselves from the radiation exposure [9].

Unfortunately, both of the previous studies only evaluated the effect of photons and beta particles, unlike the proton particles primarily found in space. There are few studies evaluating the impact of proton irradiation on plant growth, though their primary objective is to potentially improve harvest yields of crops grown on Earth. In a study conducted at the Tata Institute of Fundamental Research in India, rice was irradiated with proton particles at doses ranging from 50 Gy to 500 Gy [9], which is dramatically higher than the ~0.5 Gy to which the astronauts would be exposed on their ~260 day journey to Mars. Germination rate showed a linear decrease with increasing dose. Additionally, there was a retarded plant growth after germination with higher doses. Another study was conducted at the Cuza University in Romania on barley seeds [11]. A proton beam at the Joint Institute for Nuclear Research in Russia was used to irradiate barley seeds at doses ranging from 3 to 5 Gy. The seeds' growth and various biochemical properties were then studied and analyzed. The results showed that increasing doses resulted in decreased lengths of the barley seedlings, with the lowest dose resulting in a 1.4%

decrease and the highest dose resulting in a 5.1% decrease. There was also a significant decrease in the growth rate of the seeds after exposure to radiation and salt stress together. Interestingly however, low doses of radiation stimulated seedling germination, particularly in the presence of saline stress in the soil. Their subsequent study on wheat seeds using 171 MeV proton beam noted a decrease in the mitotic index of the seed cells, and tenfold increase in genetic aberrations, though there were no changes in weight or lengths of the seedling roots and shoots [12].
There is therefore significant uncertainty about how well seeds and crops will tolerate proton space radiation, both on the way to Mars and once we set up long term settlements. This study focuses on the effect of proton irradiation on radish seeds, and will help to address the gap in research on the response of various plants to proton irradiation at different radiation dose levels.

Research Question

Does irradiation of radish seeds with different doses of proton particles affect their 1) germination rate and 2) plant growth and mass?

Methods–Literature Search

A literature search was performed primarily using the PubMed database from the National Library of Medicine (pubmed.ncbi.nlm.nih.gov). Initial broad interest was the effect of space radiation on plants. Terms such as “plant”, “crop”, “irradiation”, “proton”, “space radiation”, and “Mars” were used. Abstracts of the resulting entries were reviewed for relevance to the broad research topic. Separately, a Google Scholar website (scholar.google.com) was used with similar search parameters. Finally, Google search was performed with similar parameters, and resulting web pages were reviewed. These included a mix of web pages for NASA, academic institutions involved with space radiation research, as well as articles from media companies such as Science News or CNN, and space-related corporations such as Northrop Grumman. These were reviewed for relevance as well. The main focus was on published academic research literature as the primary source of research findings. After the initial broad literature review, the research question was narrowed to address a knowledge gap in the scientific literature as described in the Introduction section and the Plant Material section.

Plant Material

This research was conducted using radishes of the Cherry Belle variety (*Raphanus sativus*) supplied by the Ferry-Morse Seed Company, and purchased locally at Lowe’s, a retail company. Radishes were chosen not only because of the convenience provided by their rapid growth and maturation, but also because they have been previously subject to studies by NASA aboard the International Space Station. On November 30, 2020, astronaut Kate Rubins harvested 20 fresh radishes grown entirely in space aboard the space station (Figure 1) [13]. This experiment confirmed the ability for radishes to grow in microgravity, which is a necessity for long-term space missions. They were selected by NASA because their quick growth, nutrition requirements, and genetic similarity to *Arabidopsis* (a genetically well-characterized plant

frequently studied in microgravity) make radishes a good test plant for long-term missions, such as those to Mars [14]. Additionally, their potential for Martian growth is being characterized in NASA's "Martian Gardens" in a collaboration with Florida Institute of Technology, where simulated Martian soil conditions are used to help scientists determine the best crops to grow on Mars [13]. Of note, there are only two academic studies which evaluate the response of radish seeds to photon radiation. Researchers in Egypt performed a field experiment where radishes were irradiated with 10 Gy to 80 Gy of photon radiation to attempt to improve harvest yields, and noted increase in number of leaves, leaf length, roots length, and root diameter with lower doses, but reduction in all the characteristics with higher doses [15]. Similarly, researchers from Brazil irradiated radish seeds with 2.5 Gy to 10 Gy dose, and noted 2-6% increase in root weight with lower doses but a decrease in root weight with higher doses [16].

Figure 1. Radish seedlings growing on the International Space Station [13].

We purchased three packets of Cherry Belle radish seeds, with 150 seeds each. The seeds were then randomly split into four separate groups of 100 seeds each (Figure 2). Each of the groups were placed in plastic Ziploc bags and exposed to a different dose of proton radiation prior to being sown.

Figure 2. Cherry Belle radish seeds being prepared for radiation

Proton Radiation Exposure

The seeds were irradiated using a Mevion S250 proton therapy system in the Radiation Oncology Department at Orlando Health, a local hospital system (Figure 3). The proton system is used during workdays for treatment of cancer patients; the seeds were irradiated on a weekend.

Proton particles had 250 MeV (mega electronvolt) energy, with a range of 38 cm in water. The flat portion of the proton dose curve before the Bragg peak end of range was used, because space protons will likely affect seeds by passing through rather than stopping inside them due to their high energy nature. The first group served as a control and was not irradiated (0 Gy). The remaining three groups were irradiated with 0.5 Gy, 10 Gy, and 100 Gy, respectively. A Gray (Gy) is a standard unit of radiation dose, representing an absorbed energy per unit mass of tissue. The first dose level (0.5 Gy) was selected because that is approximately the dose to which the astronauts and the seeds would be exposed on their seven month journey to Mars [17] . The second and third dose levels were selected to establish a range of responses to radiation. For comparison, cancer patients are typically treated with doses up to 70 Gy. All of the seeds were given the entire radiation dose in a single setting. After the seed batches were irradiated, 24 "best" seeds were manually chosen to plant per group. These were selected based on their appearance, in terms of larger size and rounder look, in order to minimize chance of growth variation as a function of seed quality rather than radiation effect. After irradiation, the seeds were contained within the radiation vault for 48 hours to ensure the levels of radiation emitted by the radishes were no longer at a dangerous level to handle.

Figure 3. Mevion S250 proton radiation therapy system at Orlando Health. Seeds were placed in the beam path on top of the blue solid water block.

Growth Conditions

Two self-watering greenhouse kit trays produced by Jiffy Group were used to contain the seeds during their growth. Each tray consisted of 70 peat pellets, arranged in six rows of twelve columns. Two of the corners did not contain any pellets for water access. The plastic nature of the trays prevented leakage and allowed for each of the pellets to be watered evenly.
The trays were each filled with one inch of tap water 24 hours prior to planting to prepare the pellets for the seeds.

The irradiated radish seeds were inserted in the center of each of the pellets; each contained one seed, which was planted at a depth of one centimeter deep from the surface (Figure 4). Exposure and intensity of sunlight on Mars varies substantially from that on Earth, so crops will most likely be grown indoors without exposure to sunlight. To simulate these conditions, the trays were placed in a windowless room to prevent any potential influence of sunlight on the growth of the radishes. Grow lights produced by Ferry-Morse were placed at a height of about one foot above the trays, and were kept on throughout the duration of the experiment. The self-watering nature of the trays allowed for greater flexibility in ensuring the plants were provided with sufficient water. The water level within the trays was monitored; the level was kept at a height of one inch above the bottom of the tray. The water used was purely tap water - no additional nutrients were added.

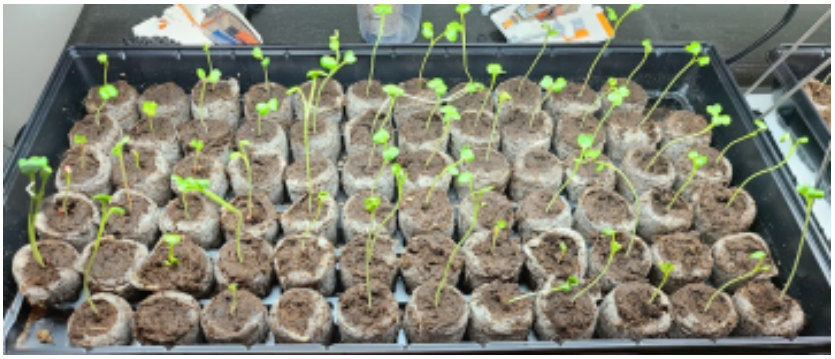


Figure 4. Greenhouse tray with radish seed germination

Data Collection and Statistical Analysis

The number of pellets with sprouts was counted daily to determine the germination rate. Final germination rates were calculated at the conclusion of the experiment. The length of the longest leaf was measured with a ruler. Radish plants were harvested 7 weeks after planting, and the weight of the total plant including the radish bulb was measured with a scale, as well as the weight of the radish bulb itself (Figure 5). The measurements were analyzed using statistical approaches. Fisher's Exact test was used to evaluate germination rate. Parametric and non-parametric statistical testing was performed, including the Mann Whitney U and Friedman tests. $P < 0.05$ was used for determining statistical significance. Analysis was performed using SPSS 27.0 software.

Figure 5. Harvested radish plant. Descriptive variables were collected at harvest

Results

The germination rate for each dose level of 0 Gy, 0.5 Gy, 10 Gy, 100 Gy was 78%, 92%, 83%, and 83% respectively. The p value was 0.47, which was not statistically significant (Table 1).

Dose	0 Gy	0.5 Gy	10 Gy 100 Gy	Total
Seeds Planted	23	24	23 24	94
Plants Grown	18	22	19 20	79
Proportion (%)	78%	92%	83% 83%	P = 0.47 (NS)

Table 1: Plant germination rate. NS = not statistically significant.

The mean number of leaves was 4.8, 5.8 , 4.8, and 5.5 respectively, which was not statistically different (Table 2). Because the data was not normally distributed, the corresponding interquartile ranges are provided (Figure 6)

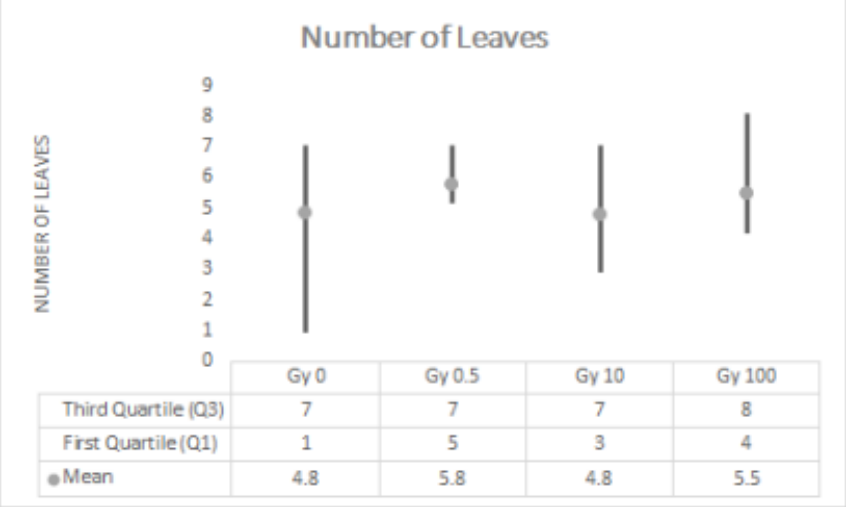


Figure 6: Number of leaves of control condition versus three experimental conditions. Data expressed with symbols for the mean and interquartile intervals.

The mean leaf length was 130.8 mm, 106.8 mm, 111.3 mm, and 124.2 mm, respectively, which was not statistically different (Table 2). Because the data was not normally distributed, the corresponding interquartile ranges are provided (Figure 7)

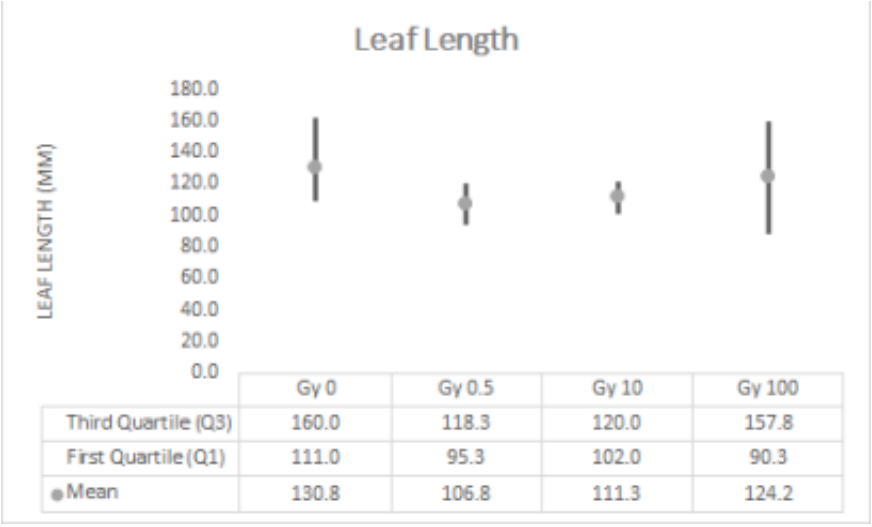
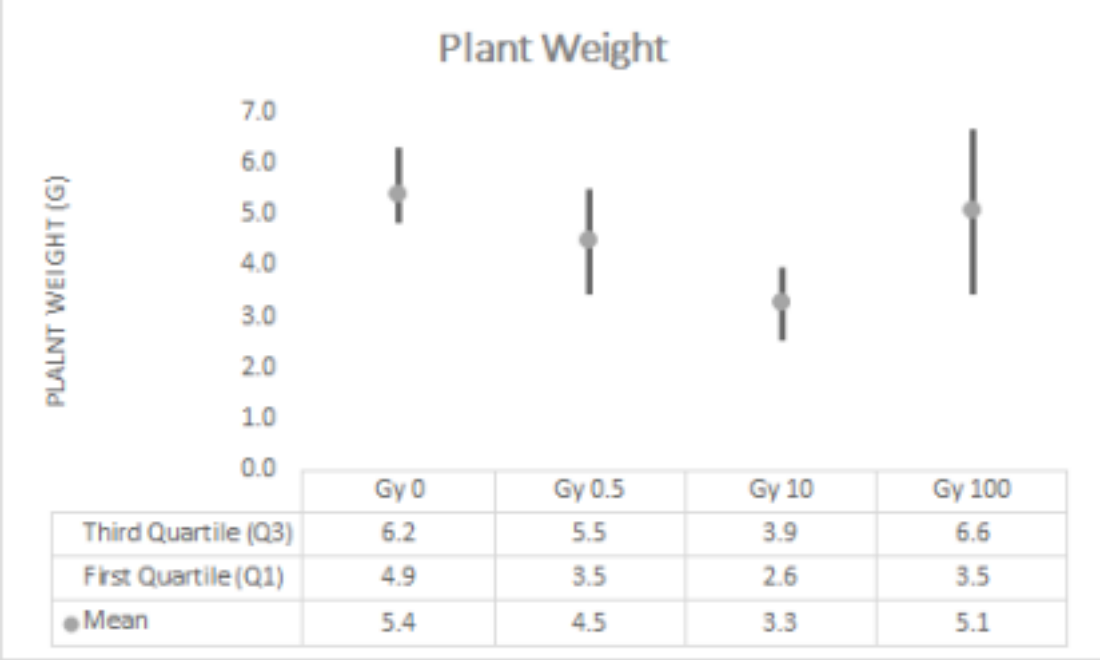


Figure 7: Mean leaf length of control condition versus three experimental conditions. Data expressed with symbols for the mean and interquartile intervals.

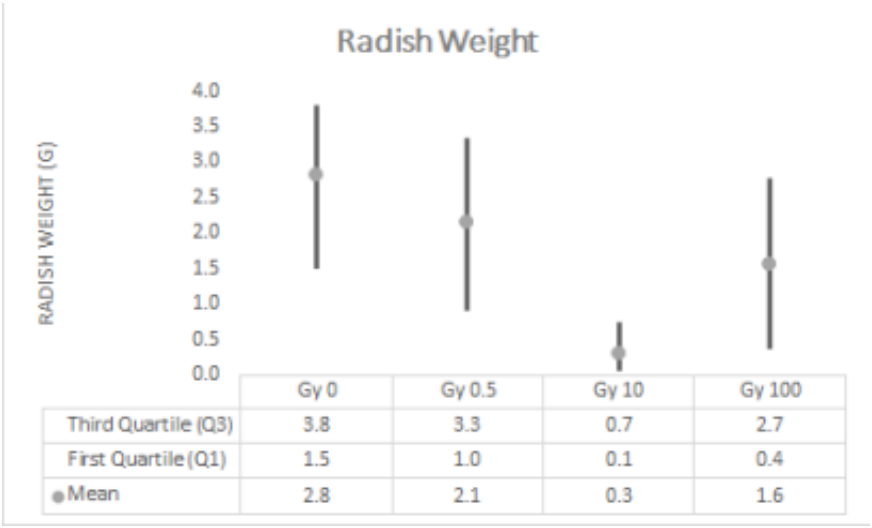
The mean plant weight was 5.4 g, 4.5 g, 3.3 g, and 5.1 g, which across the four groups was not statistically different. Of note, there was a statistical difference in the plant weight between the control and the 0.5 Gy group ($p = 0.044$), as well as between the control and the 10 Gy group ($p = 0.002$). However, there was no statistical difference between the control and the 100 Gy group ($p = 0.8$), and the 4-way comparison was overall not statistically different (Table 2



	Gy 0	Gy 0.5	Gy 10	Gy 100
Third Quartile (Q3)	6.2	5.5	3.9	6.6
First Quartile (Q1)	4.9	3.5	2.6	3.5
Mean	5.4	4.5	3.3	5.1

Figure 8: Mean plant weight of control condition versus three experimental conditions. Data expressed with symbols for the mean and interquartile intervals.

The mean radish bulb weight was 2.8 g, 2.1 g, 0.3 g, and 1.6 g, which across the four groups was not significant. Of note, there was a statistical difference in the plant weight between the control and the 10 Gy group ($p < 0.001$), as well as between the control and the 100 Gy group ($p = 0.01$) (Table 2 and Figure 9)



	Gy 0	Gy 0.5	Gy 10	Gy 100
Third Quartile (Q3)	3.8	3.3	0.7	2.7
First Quartile (Q1)	1.5	1.0	0.1	0.4
Mean	2.8	2.1	0.3	1.6

Figure 9: Mean radish bulb weight of control condition versus three experimental conditions. Data expressed with symbols for the mean and interquartile intervals.

Dose	0 Gy	0.5 Gy	10 Gy	100 Gy	Statistical significance
Number of leaves (count)	4.8	5.8	4.8	5.5	NS
Leaf length (mm)	130.8	106.8	111.3	124.2	NS
Plant weight (g)	5.4	4.5	3.3	5.1	NS

Radish bulb 2.8 2.1 0.3 1.6 NS weight (g)

Table 2: Plant descriptor summary. NS = statistical comparison is Not Significant in a 4-way groupwise comparison at the $p < 0.05$ level. However, there were some differences among individual group comparisons.

Discussion and Implications

This study was conducted to determine the impact that varying doses of proton radiation may have on the growth of radish seeds. There was no statistically significant difference in the rate of seed germination among the different groups. However, the 0.5 Gy dose level had a higher germination rate than both the control and the higher dose levels. Seed germination is a very delicate process that requires specific environmental conditions to be present, as individual seeds have only a limited amount of stored energy available to successfully grow and develop. The seed coat, which protects the seed embryonic cells, needs to allow absorption of water from the environment to start the germination process, before metabolic activation and ultimately radical protrusion of the root and stem through the seed coat can occur [18]. In agriculture, the concept of seed priming is to pre-treat the seeds, typically by soaking them in water or a solution, to initiate and enhance the germination process and ultimately enhance harvest yields. Various seed priming techniques have been developed, starting in ancient Greece when Theophrastus documented around 300 B.C. that soaking cucumber seeds in water would improve their germination [19]. Over the past several decades, further techniques have been developed in agricultural production, which include osmopriming, magnetopriming, nutripriming, antioxidants, phytohormones, chemical priming, and of particular relevance to this study ionizing radiation priming [20]. Proton radiation has been postulated to cause perforation of the seed coat and create micropores to facilitate water absorption at the start of germination. Deoli and Hasenstein irradiated *Brassica rapa* seeds with low energy proton ions (1 MeV to 3 MeV) and found that damage of the seed coat with 1 MeV protons led to faster germination and initial seedling growth, since the protons stopped at the thickness of the coat and did not penetrate into the seed embryo [21]. However, germination percentage decreased with increasing dose and with

proton energies >1 MeV that allowed the proton particles to penetrate through the seed coat. For comparison, our proton energy was 250 MeV and the protons passed through the entire seed, while the cosmic ray protons can carry energies even thousands of times higher, in the GeV range. Once the protons pass through the coat, and possibly improve the permeability, they may also start to affect the plant cells inside the embryo and their DNA, cause unfavorable mutations, and ultimately lead to lower plant growth or even death. This biphasic response is known as hormesis (Figure 10), where increasing dose of exposure initially causes a beneficial effect but eventually starts to cause adverse / toxic effects [22]. Therefore, there appears to be some evidence of germination hormesis in our data, but due to low sample numbers and small power of the study, the results were not statistically significant. Our data support the results from the barley irradiation study by Oprica discussed in the introduction, where low doses of proton radiation stimulated germination [11].

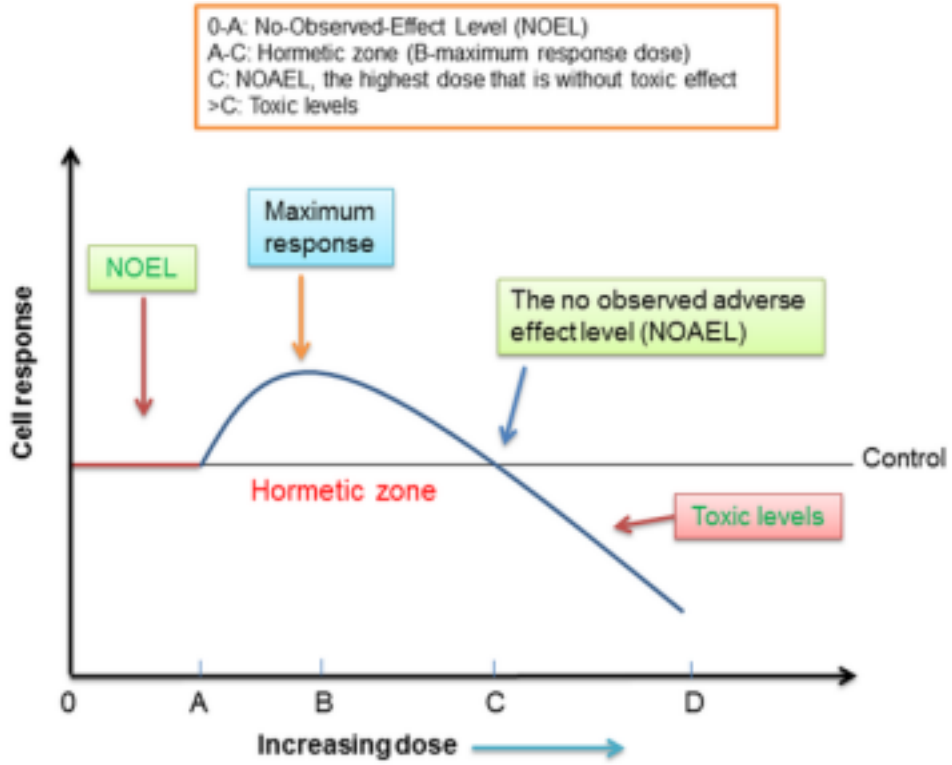


Figure 10: Hormesis concept, where increasing dose of exposure, whether to chemicals or radiation, initially causes no observed effect (NOEL), then causes a beneficial effect (hormesis), and eventually starts to cause adverse / toxic effects.

There was also no statistically significant difference in various plant characteristics among the four groups in our study. In terms of the leaf canopy, evaluated as both the number of leaves and maximum leaf length, there was no significant difference on a 4-group comparison, or between the control and the individual dose groups. However, there was a difference visually, where the higher dose group leaves looked thinner, narrower, and not as healthy, though this was

not captured in our measured data. There were some inter-group statistical differences in both plant weight and radish weight. Specifically, there was a decrease in plant weights from control (0 Gy) to the 0.5 Gy to the 10 Gy group, which were individually statistically significant. But the 100 Gy group had higher weight, and therefore the overall comparison between the control group and the irradiated group as a whole was not significant. Similarly, there was a lower mean radish bulb weight at the 0.5 Gy level, which did not reach statistical significance, but the lower weights at 10 Gy and 100 Gy dose levels were statistically significantly smaller. Given that there is an inverse relationship between higher radiation dose and plant mass in the existing literature that we reviewed in the Introduction section, we suspect that this is true in our data as well, and that higher doses of proton particles have a negative effect on radish plant growth and bulb formation, though higher statistical power would be needed.

Even though there was no statistically significant difference in either the germination rate or the plant characteristics and their biomass, our data potentially raise a question about the future success of radish growth on the way to Mars and once there. Our low dose group (0.5 Gy) received a similar amount of radiation likely to be experienced on the way to Mars, and also while on Mars for a duration of one cycle, before journey back to Earth becomes feasible from a planet alignment perspective. The 10 Gy dose and 100 Gy doses are likely well in excess of what the seeds would truly experience, even potentially with solar storms. In the 0.5 Gy group, we saw two opposing effects of the proton radiation. On the beneficial side, there is the potentially improved germination rate, where proton therapy may jump start and improve the germination process itself, when the embryo starts to grow through the hard shell and into the surrounding soil. On the negative side, the proton particles may damage the DNA of the internal plant embryo cells, similar to what happens with human irradiation, and they may ultimately not grow as well into the mature plant, with more mutated appearance and lower biomass of the plant and radish bulb. This is potentially of concern, as the purpose of the radish farming would be to produce food supply from the radish bulb.

The dose response curve evaluating the amount of radiation and its impact on either germination or plant growth is still not well established, especially in the low dose range that is relevant for space flight and Mars settlements. It will be important to carefully evaluate the lower doses that are more relevant to the space program, which are in the 0.1 Gy to 1 Gy range, rather than the doses that have been subject of academic studies in plant irradiation for genetic mutation engineering to improve yield, which were in the 10 Gy to 100,000 Gy range. Going forward, I plan to engage with NASA about their research priorities and hopefully collaborate to develop a crop proton irradiation program to help evaluate effects of space radiation to help humanity settle our solar system. In the interim, studies that I would like to pursue include repeating the current study with larger seed numbers and lower radiation doses, to improve the power of the study. I am also interested in evaluating chronic low dose radiation, which would be more similar to the exposure in space, though with the clinical proton therapy system used to treat cancer patients daily, this may be logistically challenging. I am also interested in evaluating different plants that astronauts could farm on Mars, including potatoes that Dr. Mark Watney farmed in the science

fiction movie The Martian, and which served as the inspiration for this project (Figure 11). Finally, it is not clear how radiation may impact the fertility or sterility of future crop generations. If the astronauts are to successfully establish a long term colony on Mars, the plants need to be self-renewing, and continue to produce viable progeny in each subsequent harvest.

Figure 11. Fictional Dr. Mark Watney growing potatoes in a greenhouse on Mars in the science fiction movie The Martian.

Study Limitations

There are several limitations in my study. First, this was a pilot study to demonstrate the ability to technically irradiate seeds with various doses of clinical grade proton beam radiation, and the number of seeds in the study was relatively low. This may have impacted the power of the study to provide meaningful statistical conclusions. Second, the study was performed using a one-time radiation exposure, whereas the seeds en route to Mars would be exposed to a low dose but chronic cosmic radiation. From a radiation biology perspective, there are some differences in how cells respond to the two exposure rates, and while there is relatively limited published research on plant radiobiology, there is extensive medical literature evaluating human exposure to nuclear power plant accidents as well as treating cancer patients with various forms of radiation therapy. During one-time exposure, all the radiation damage to the cell, both to the structural elements and to the DNA, happens at once, and the cell may become overwhelmed and die, which may take hours to days or even weeks, depending on the amount of radiation received. On the other hand, with chronic low dose radiation, the damaged cells can potentially be repaired over time. Or, the radiation exposure can continue to accumulate over time and eventually lead to the cell's permanent genetic damage. It is therefore important to simulate not only the type of radiation (proton versus photon versus alpha/beta particles) and the total exposure dose, but also the dose rate and how rapidly the cells in the seed are exposed to the radiation. Third, radishes are a cool season crop, and in our state the weather temperatures may have been too warm for their optimal growth, even though we planted them in the winter, although this should not have impacted one group more than another group, as they were all

grown in the same environment. Finally, I am not a very good farmer and some differences in growth may have been attributed to my relative inexperience with growing radishes and plants.

Conclusion

The primary research question of this study was whether irradiation of radish seeds with different doses of proton particles affects their 1) germination rate and 2) plant growth and mass? Our results show no statistically significant evidence that proton particles at 0.5 G, 10 Gy and 100 Gy dose levels affect either radish germination rate or the plant growth and mass. Despite this absence of statistical differences, there seems to be a trend indicating that radiation may improve germination at low doses, but may negatively impact plant characteristics including plant weight and radish bulb weight at both low and high doses. Further research is needed to more precisely evaluate this impact. Nevertheless, I am cautiously hopeful that astronauts will ultimately be able to farm radishes on the way to Mars and once there.

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Immunohistochemistry in the Detection of Lung Cancer Cells By Suhkyung Yu

Introduction

In today's world, almost everyone will be affected by cancer; among the different types, lung cancer has one of the highest mortality rates even though treatments exist. The building blocks of this illness are so-called cancer cells, the smallest structural and functional unit causing the lungs to possess cancer. Cancer cells do not simply "invade" an organ, they attach and bind to each other to form a distinct type of tissue in the lungs. These attached cells are called cell adhesion molecules (CAMs), which are a subset of cell surface proteins involved in the binding of cells in a process called cell-cell adhesion. CAMs help cells stick to each other and their surroundings, maintaining the tissues as they facilitate interactions between the cells to function effectively. CAMs can be classified into four major types: immunoglobulin, integrins, cadherins, and selectins. These types all bind or regulate cells, which have specific functions in the human body. In the case of lung cancer, CAMs have been found to play a significant role in the development and metastasis of the cells. Lung cancer begins in the lungs and may spread to lymph nodes or other organs in the body, such as the brain. The cancer cells break away from where they first formed, travel through the blood, and form new tumors (abnormal masses of tissue). CAMs have been found to be impaired in this formation, leading to changes in cell migration, invasion, and the growth of new blood vessels known as angiogenesis. Due to their microscopic sizes, the way to detect CAMs in lung cancer has complicated the field and delayed the development of diagnosis technology. The challenge is to evaluate one of the "innovations" made to detect cell adhesion molecules and cancer cells during the progression of lung cancer. This can ultimately be used to benefit and conveniently diagnose cancer by looking through tissues and existing molecules in the lungs.

Analysis

To detect CAMs in lung cancer, Albert Coons, an American immunologist implemented a technology called "immunohistochemistry" (IHC), a technique that utilizes antibodies or proteins to detect specific cells in tissue samples. IHC is especially useful in detecting the expression of CAMs in tumor tissues from lung cancer. The development of IHC made it possible to visualize the localization of specific cellular components within cells. The IHC comprises two main processes: Tissue fixation and Tissue processing. Tissue fixation is the process where tissue samples are first frozen with a common fixative called formalin, which preserves cell structures. It is the most crucial step in the preservation of tissues because it is possible to observe consistent characteristics in tissue sections that allow patterns and morphological features. In the step of tissue processing, the fixed tissue samples are dehydrated and embedded in paraffin wax, then cut into thin sections. The tissues may require further dissection to select appropriate areas, especially during diagnosis. Paraffin wax is immiscible with water, so most of the water in a tissue sample must be removed before it can be infiltrated with wax. Those infiltrated specimens finally get conserved and investigated without being physically or chemically converted. In the

case of lung cancer, IHC is used to identify the biological markers or subtypes, such as adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and neuroendocrine tumors. For example, when detecting small cell carcinoma, IHC can be used to detect two different proteins called synaptophysin and chromogranin A. Synaptophysin is a protein that is composed of small round cells, one of the features of small cell carcinoma. Through tissue fixation, a tissue sample from a lung tumor is frozen and embedded in paraffin wax. The sample is then cut into thin sections and placed onto slides. Synaptophysin is injected into these specimens, treating the tissues with an antibody that is tagged with a color marker. If the tissue contains small cell carcinoma, the synaptophysin antibody will bind to the protein and produce a visible signal that can be detected under a microscope. Chromogranin A is used with synaptophysin in IHC and is also injected in a similar process of tissue fixation. Chromogranin A will also bind to the antigen and produce a visible signal that can be detected. CAMs in lung cancer cells were readily discovered through immunohistochemistry, leading to advancements in diagnosis and prognosis technology.

Discussion–Strengths

There are two major benefits of IHC in the diagnosis of lung cancer: affordable procedure, and precise localization. First, IHC can be performed with few resources, as it involves a fundamental and affordable process to detect CAMs in tumor tissues. IHC is relatively easier than other prognosis techniques, as they include isolation and extraction of proteins from diversified cells. In contrast, IHC uses pre-processing steps of tissue fixation, tissue processing, and antigen retrieval to perform directly on tissue samples. IHC also establishes standardized protocols when it detects a biological mark or subtypes of lung cancer during its performance. This makes researchers and clinicians regard the technology as easier to use in their investigation of CAMs for lung cancer. Second, IHC is a powerful technique to study the precise localization and regulations of cells in tumor tissues. IHC identifies changes in CAM expression, as they detect different stimuli such as distortion and cell invasion when examining lung cancer cells. IHC also visualizes CAM expressions, which provide information on the regulation and abundance of cell adhesion molecules in different tumor tissue types. IHC may eventually help researchers understand the role of CAMs in lung cancer progression, as the technology simply documents cancer molecules such as adenocarcinoma in tissue samples.

Limitations

While IHC can be used for tissue preservation and CAM regulations in an advanced way, there are features that IHC must improve to contribute to diagnosis technology. The two primary limitations are the following: limiting sensitivity and the production of false-positive results. First, IHC is highly vulnerable to generating results that can either be false-positive or false-negative. There are several scenarios when the antibodies sometimes cross-react with other molecules in the tissue. Due to this interaction, the antigen can be lost or be in a low concentration during tissue processing or fixation, and IHC will not be able to detect any cancer

cells. These variables may cause IHC to have false-positive results, affecting the diagnosis of lung cancer in patients. IHC also produces false-negative results, especially when the antibodies fail to recognize the intended target antigen in particular tissue samples. This can occur mostly from genetic variation, a process when the genes in the tissue samples modify amino acid changes. These changes alter the epitope recognized by the antibody, causing the antibody not to bind to the antigen. These uncertainties create false-negative results, making the process of detecting lung cancer cells exceptionally challenging. Second, IHC associates with limited sensitivity, as it but often fails to identify low-abundance antigens in tissue samples. If the antigens have a low concentration or are expressed at low levels in the tissue sample, IHC does not detect CAMs or any other protein. This leads to underestimation, failing to diagnose harmful cells or biological markers in the case of lung cancer.

Conclusion

IHC takes a crucial role in treatment planning and diagnosis of lung cancer, as it detects CAMs and subtypes from tumor tissues. Given the fact that it still needs to improve in certain areas, the technology must be extended to provide medical assistance for patients such as personalized medicine and early detection. IHC should be advanced to precisely detect CAMs and antigens despite their lower concentrations in tissue samples. Also, referring to the limitations shown above, IHC might have to prevent false-negative and false-positive outcomes from happening by not letting antigens and samples cross-react or be genetically modified. In future generations, IHC can help apply the information of biomarkers associated with cancer, and design personalized treatment plans for lung cancer patients based on the subtype or CAM profile. As the IHC detects lung cancer from antigens and tissue preservation, it can also become a valuable tool in the clear and early detection of lung cancer. When the IHC advances in these ways, it will have the potential to revolutionize the diagnosis of lung cancer, enabling even small specific biomarkers in tumor tissues, and aiding the early detection that leads to better treatment outcomes over the next 10 years. The earlier the detection of the presence of lung cancer, the better the individual's or patient's chances of survival and complete treatment. Based on this perspective, the significance of diagnosing tumor cells in lung cancer through IHC is being publicized as a global responsibility of health.

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Enhancing Human Rights and Sustainable Practices in Cobalt Mining: The Role of Supply Chain Due Diligence By Zachary Deutsch

Abstract

Artisanal and small-scale cobalt miners in the Democratic Republic of Congo (DRC) face numerous human rights abuses, including poor working conditions and child labor exploitation. As the DRC remains a global leader in cobalt production, driven by the increasing demand for lithium-ion batteries, concerns over the health and well-being of these miners have escalated. While previous attempts to address the issue, such as Law No. 007/2002, fell short, this research paper proposes a solution centered around international legislative regulations requiring supply chain due diligence and responsible cobalt standards. This research paper examines the effectiveness of supply chain due diligence through a case study of two artisanal and small-scale mining (ASM) sites in the DRC. Results reveal that implementing due diligence significantly curtails common human rights violations, such as child labor, by enforcing strict age control systems. Moreover, supply chain due diligence improves health and safety conditions in ASM mines, thus reducing occupational accidents and mitigating health risks associated with elevated cobalt exposure. Despite a counterargument questioning the efficacy of due diligence initiatives, the paper highlights the adverse welfare impacts of eliminating ASM mining, emphasizing the need for sustainable solutions. The proposed implementation involves an international cobalt supply chain management system, promoting ethical and safe standards for cobalt mining. While short-term challenges may arise during the certification process, strict enforcement of supply chain due diligence promises long-term benefits for ASM cobalt miners in the DRC. By safeguarding their human rights and improving working conditions, this solution aims to strike a balance between economic demands and social responsibility in the cobalt mining industry.

Introduction

Artisanal and small-scale cobalt miners in the Democratic Republic of Congo (DRC) experience human rights abuses through poor working conditions and child labor exploitation. As defined by the National Minerals Information Center, cobalt is a metal mined as a byproduct of copper or nickel (National Minerals Information Center). Although many countries produce cobalt, the DRC is a global leader in cobalt production. According to the European Commission, a politically independent executive arm of the European Union, "The DRC produces about 60% of worldwide cobalt" (European Commission). Cobalt is widely used in producing goods, including lithium-ion batteries for smartphones, computers, and electric vehicles, for which demand is growing. Specifically, the electric vehicle industry heavily relies on cobalt production. According to the Columbia Center on Sustainable Investment, a university-based applied research center and forum dedicated to studying, practicing, and discussing sustainable international investment, lithium-ion batteries are an "integral component to powering electric vehicles" (Ali, Saleem, et al). Furthermore, Raphael Deberdt and Philippe Le Billon, professors of anthropology and geography, respectively, at the University of British Columbia, state that

electric vehicle production is rising because of climate change initiatives (Deberdt and Philippe Le Billon). Therefore, cobalt production in the DRC is essential in both global economies and climate change technologies. However, this recent evolution comes at the cost of the health of artisanal and small-scale cobalt miners in the DRC. The International Labor Organization defines artisanal and small-scale mining (ASM) as "mineral extraction undertaken by individuals, small groups of individuals, or cooperatives working with hand tools or elementary forms of mechanization" (Hentschel et al.). As nations attempt to remain resilient in the fight against climate change, they also become tolerant of poor ASM conditions. Tomas Chamorro-Permuzic and Derek Lusk corroborate this idea in *The Dark Side of Resilience.* They claim that "when resilience is taken too far, it may focus individuals on impossible goals and make them unnecessarily tolerant of unpleasant or counterproductive circumstances" (Chamorro-Permuzic and Derek Lusk). Addressing climate is a necessary goal, but it must not infringe upon the human rights of ASM cobalt miners to achieve this goal. Célestin Banza Lubaba Nkulu, a professor of public health at the University of Lubumbashi, claims, "A substantial proportion (estimated at 15-20%) of cobalt in the DRC is being extracted by artisanal miners" (Célestin Banza Lubaba Nkulu et al., 2018). Also, due to the increasing demand for cobalt to make electric vehicles, children have been employed to extract cobalt. Currently, "12.65% of the mining workforce living in mining communities is below the age of 18" (Benjamin Faber et al.). Ultimately, ASM cobalt miners in the DRC are vulnerable to severe health conditions because of the hazardous ASM conditions. International legislative regulations requiring supply chain due diligence and responsible cobalt standards should be implemented to solve this issue of human rights abuses, poor working conditions, and child labor exploitation among ASM cobalt miners in the DRC.

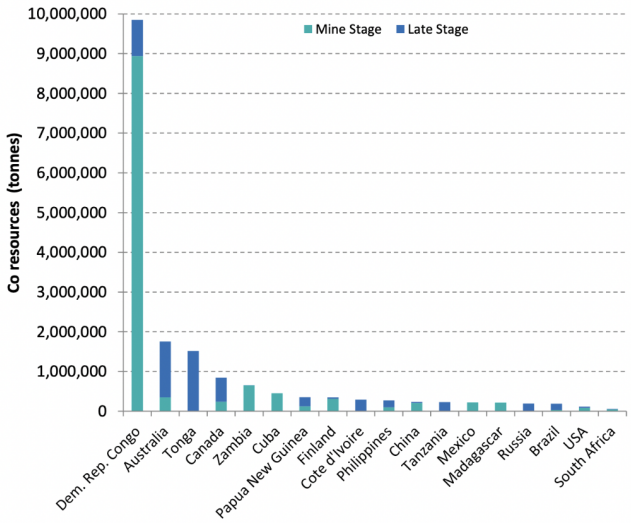

Figure 1. Illustrates 2023 cobalt deposits (in tonnes) by country, including mine stage and late stage.

Note. European Commission. (2023). *Critical raw materials.* Single-Market-Economy.ec.europa.eu. https://single-market-economy.ec.europa.eu/sectors/raw-materials/areas-specific-interest/critical-raw-materials_en

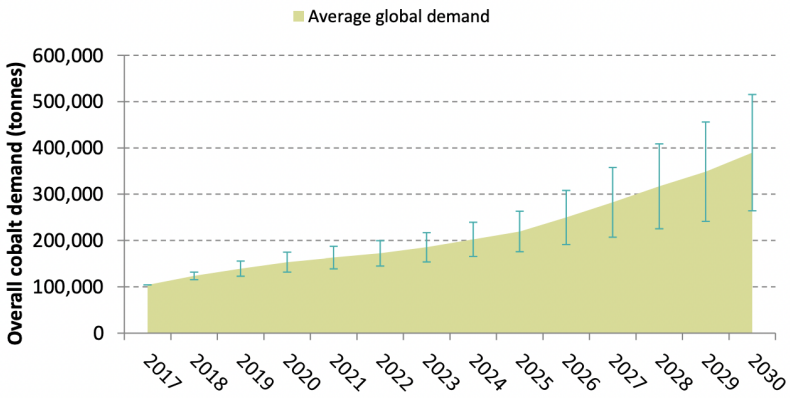

Figure 2. Displays global cobalt demand (in tonnes) from 2017 to 2030.
Note. European Commission. (2023). *Critical raw materials*. Single-Market-Economy.ec.europa.eu. https://single-market-economy.ec.europa.eu/sectors/raw-materials/areas-specific-interest/critical-raw-materials_en

Previously Attempted Solution

Law No. 007/2002, implemented by President Joseph Kabila, was the primary solution to improve the disadvantageous conditions for artisanal and small-scale miners. Filipe Calvão, an anthropology and sociology associate professor at the Geneva Graduate Institute, describes, "This 2002 law aimed to formalize ASM and fuel growth of DRC's mining industry through the creation of artisanal mining zones" (Calvão et al.). To operate legally under this new law, ASM miners were required to obtain a mining permit to mine in designated areas. However, the law also included some harsh restrictions. Calvão notes, "Should the permit be lost, destroyed, or stolen, authorization for artisanal mining would not be reissued, adding to the vulnerability of miners." Additionally, the 2002 mining code stated that ASM zones should be developed where the "technological and economic factors are not suited for the site to be industrially exploited." Thus, ASM zones would be limited to the least profitable areas with poorer cobalt deposits. Ultimately, the passage of Law No. 007/2002 failed to formalize ASM because it increased the financial burden on ASM cobalt miners and reduced their mining security.

Solution Claim One

International legislative regulations requiring supply chain due diligence based on responsible cobalt standards and mineral traceability systems would help to address human rights abuses. Supply chain due diligence occurs at ASM mines to ensure the safety and ethics of ASM. Lucia Mancini, a professional research councilor at the Slovenian National Building and Civil Engineering Institute, assesses the impacts of supply chain due diligence in ASM for cobalt through a case study of two ASM sites in the DRC. The first case of supply chain due diligence is *Better Mining,* an ASM site that regularly monitors working conditions and incident reports (Lucia Mancini et al.). Additionally, access to this site is only possible through dedicated doors, which are constantly supervised. To enter, miners must provide a document certifying they are over 18 years old. The second case of ASM supply chain due diligence is the *Mutoshi Cobalt*

Pilot Project, which also aims to improve safe working conditions by site monitoring and reporting information on incidents. Similarly, miners must enter through designated gates by showing their membership cards. Additionally, miners must wear personal protective equipment and closed shoes to enter the site. Overalls and hard hats are offered free of charge to the miners, ultimately ensuring the safety of ASM cobalt miners. Lucia Mancini et al. conclude that "in contrast to the baseline, where child labor is a serious risk, no cases of child labor or young adolescents working on sites have been either directly observed or reported by the Chief Security officers or miners consulted." Both pilot sites rigorously enforce age control systems to avoid the presence of minors on site. Although human rights violations are a severe risk in the ASM sector, this case study demonstrates that ASM due diligence entirely suppresses these common human rights violations.

Solution Claim Two

Mandatory supply chain due diligence also improves egregious health and safety conditions in ASM mines in the DRC. Elevated cobalt exposure (especially in children) increases the rate of birth defects and erectile dysfunction among ASM miners in the DRC (Lucia Mancini et al.). Additionally, ASM sites in the DRC exhibit hazards and report a high frequency of occupational accidents. These poor working conditions cause both mental and physical suffering among artisanal and small-scale miners. The human rights abuses faced by ASM cobalt miners in the DRC are analogous to the human rights abuses faced by Nelson Mandela, as described in Ch. 60 of *Long Walk to Freedom*. Mandela describes the difficulties that he and other Africans faced while in prison, detailing, "Prison is designed to break one's spirit and to destroy one's resolve. To do this, the authorities attempt to exploit every weakness, demolish every initiative, and negate all signs of individuality with the idea of stamping out that spark that makes us human and who we are" (Mandela). Just as the prison authorities dehumanized Mandela, ASM cobalt miners face similar human rights abuses from the poor conditions of ASM cobalt mines in the DRC. However, the case study presented by Lucia Mancini et al. reveals success in combating these mines' egregious health and safety conditions. *Better Mining* and the *Mutoshi Cobalt Pilot Project* both demonstrated that supply chain due diligence improved the health and safety conditions for ASM cobalt miners. Mancini concludes, "Compared to the baseline, the occupational health and safety conditions on both sites are significantly better as neither has recorded any fatalities during the last year and the level of risk has decreased markedly according to both miners and consulted Chief Security Officers" (Lucia Mancini et al.). Thus, regulations requiring supply chain due diligence would improve the human rights of ASM cobalt miners by eliminating the exploitation of child laborers and improving the working conditions for all ASM cobalt miners.

Counterargument

However, Christoph Vogel, a former UN Security Council expert on the DRC, suggests that supply chain due diligence may be ineffective. Vogel points out that "supply chain due

diligence initiatives have ambivalent effects on the livelihoods of local communities and that the income of artisanal miners has decreased in some areas" (Vogel et al.). There were numerous reasons for these effects. For instance, ASM mines had to shut down for long periods until certification processes were completed, authorities rarely issued clear titles for land and mining, and there was a general lack of technical and financial support for artisanal miners. Furthermore, the supply chain due diligence and traceability reforms destroyed many of the existing local regulations for ASM mining sites and frequently created tensions among different newly established mining cooperatives (Vogel et al.). One alternative solution to the ongoing human rights abuses of ASM cobalt miners in the DRC is to reduce or even eliminate ASM cobalt miners in favor of industrially mined cobalt by large-scale companies. This solution would eliminate the need for new regulations requiring supply chain due diligence.

Rebuttal

Removing ASM mining can have detrimental welfare impacts. Benjamin Faber, an associate professor at the Department of Economics at the University of California Berkeley, points out that since a significant number of households, and children, depend on artisanal mining for their income, interventions that reduce demand for artisanal mining output are likely to harm the livelihoods of children and families living in the DRC (Faber et al.). The risks are especially high because, on average, households in the DRC are poor, have limited ability to save, and are particularly vulnerable to regional demand shocks. Furthermore, since the search for additional household income is the primary reported cause of child labor, adverse shocks to ASM miners' income by forcing households to search for alternative, often less profitable activities could increase child labor in the region. For these reasons, efforts to reduce or eliminate the sourcing of ASM of cobalt risk harming many households in the DRC.

Why the Proposed Solution Is Better Than the Counterargument Solution

Although the income of artisanal miners may have slightly decreased, it is only temporary. Once artisanal mines are certified, they need not be shut down again for certification. Additionally, destroying many of the existing informal local regulations for ASM mining sites creates safety standards and regulations to ensure that all ASM mines have safe working conditions.

Implementation

International legislative regulations requiring supply chain due diligence and responsible cobalt standards can be implemented through a cobalt supply chain management system. This system would be facilitated through partnerships on a cross-country level, regulated by international trade and investment organizations. An international supply chain management system ensures an ethical and safe standard for ASM.

Conclusion

Mandatory supply chain due diligence of cobalt becomes ineffective when they are no longer enforced. It is the responsibility of countries and international organizations to enforce such regulations. However, if supply chain due diligence is enforced, it will present both short and long-term effects for ASM. In the short-term, cobalt mines may have to be shut down for certification of health and safety standards, thus resulting in temporary unemployment of ASM cobalt miners and a shortage of cobalt supply. In the long term, supply chain due diligence will improve ASM mines' working conditions and health outcomes among ASM miners. Ultimately, supply chain due diligence will improve the human rights and working conditions of artisanal and small-scale miners in the Democratic Republic of Congo.

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Low Income Students and Their Low Application Rates to Prestigious Universities By Sidharth Kasarla

Abstract

High-achieving students can be found in every economic background, however, only a small percentage of students from a less fortunate situation apply to top universities that can polish their abilities, contrary to similarly high achieving students who enjoy economic prosperity. This is odd given the fact that top universities have been noted for their generous financial aid packages and acceptance of students who are not so well off. In this paper, I will be explaining how there are multiple heuristics and biases that may affect the decisions of these students and why they do not throw their hats in the ring of selective college admissions. The biases and heuristics that I will be covering include the Status Quo Bias, the Availability Bias, and the Anchoring Effect. The Status Quo Bias is a common cognitive function that compels people to follow what they are comfortable with or are accustomed to. It can be very gripping for low-income students whose immediate family and friends may have never gone to a selective university or any university at all for that matter. Therefore, many will see it as too big of a leap for their own comfort and will stray away from schools that they have no familiarity with in any capacity. The Anchoring Effect, while it can and will affect most people, is even more dangerous to people from low-income households. The Anchoring Effect is a heuristic that engrosses those who fall under its trap as it quite often will "anchor" a person to a statement, idea, or number that may not encompass the full story. This is often the case when poorer students look at tuition prices and acceptance rates. Availability bias, while similar to the others, affects the mind through other means. Availability bias is when one conjures up beliefs and ideas based on the information and people around them, as that is what is "available". This applies to low-income students almost exactly, as many students in disadvantaged backgrounds do not have any support from their friends or family who actually know how to apply to a top university, as well as what it takes. I conclude each bias section by finding solutions to each heuristic in the way I believe will be the most practical and probable methods, which include taking advantage of the internet and alumni, schools running ads on the benefits of their institution and the nonexistent cost of trying, and having colleges help prevent people from falling for the first attention-grabbing information that one sees.

Introduction

Often seen as the "golden ticket of opportunity", colleges and universities have long enjoyed an era of observed necessity and importance towards escaping poverty and obtaining wealth. As they have occupied this position of unrivaled need in the eyes of the public, the affluent and influential have ended up gaining most of the positions in these colleges with the many benefits they can provide their children that come from being wealthy. Thus, for the last couple of decades or so, statistics have shown that the dream colleges that poor people aspire to have already been filled by those who have been rich. The percentage of students that come from

families below the poverty line has dropped from 10% to 5% at top universities (Avery 2010). But as education has become more widespread and accessible there have been people calling for colleges to do better in regard to lower-income students. To erase the stigma surrounding top universities, these institutions provide great financial aid and high acceptance rates for poorly qualified students, yet still, only a small portion of said demographic apply(Hoxby and Turner, 2013). This shows that there are reasons outside of a school's own policies that are making students of disadvantaged backgrounds not apply and that it is more so about the heuristics that these kids carry that are holding them back.

Section 1: Availability Bias

Availability bias is one that can be very hard to discern when it has taken hold of someone, however, it can be seen in almost every single person. Availability bias, or at least my interpretation of the heuristic, is when a person forms ideas or beliefs based on the information and people they have around them. It is inescapable in its essence as it is common practice to copy the people around us and gather information from them. As the famous quote goes, " Monkey see, monkey do". This line effectively summarizes the idea behind availability bias and how it is a subconscious cognitive function that humans are unable to avoid. Therefore, there should be no doubts about how availability affects kids from disadvantaged backgrounds as they learn from the people around them (ie: mother, father, friends, teachers) and they are all part of the same background. A top student cannot expect to gain help from the people around them with something that the people around them had never undergone themselves. This is in stark contrast to kids from financially well-off backgrounds who can receive the attention and help they need in these areas. 22% of students applying to top universities receive one on one counseling of some kind that is not attached to their school. (Avery 2010)[1] This is a benefit that disadvantaged students aren't able to afford, but is almost a necessity given the sheer percentage of students using this expensive tool to achieve acceptance to their dream college.(Fontinelle, 2020).[2] Tools like these that disadvantaged students are forced to pass on due to sheer expense are one of the many reasons they decide not to apply in the first place.

On the topic of counseling and outside help, attention should also be brought to school counselors, as in theory, they are and should be completely free as they are provided by public schools all over the country. However, this is far from the case. We must remember that these kids come from not only low-income families but low-income neighborhoods and communities as these two are most often transitive. In the entire country, it is estimated that for every full-time counselor, there are 315 students to go along.[3](Avery, 2010). Counselors like these are strained by the sheer amount of students that they will inevitably never get to go through in

[1] Data was gathered by The Independent Educational Consultants Association, unassociated with Christopher Avery himself, rather a statistic taken from his paper.

[2] The following website states that a 1 hour meeting can cost $250, with a package of 1 year on average is $6000, thus why I called it expensive. https://blog.massmutual.com/post/college-admissions-counselors:-weighing-the-price

[3] Data gathered by study created by the National Center for Education Statistics (NCES) and this statistic was taken from the Avery paper.

college-related issues. This is because Counselors in public schools have different roles than those of a one-on-one college counselor or a private school college counselor.[4](Avery 2010) Counselors at public schools are the guides of every single aspect of the school for their students. They are expected to work with students with family issues, bullying, school drama, and much, much more. It would be a prayer for underfunded schools to have underpaid counselors get to every single child and help them with the college admission process.

As stated when defining what availability bias is and how it pertains to disadvantaged students, it is imperative to speak on the role of parents, friends and other familiars and why they are not of much help. Studies suggest that parents of disadvantaged students are unable to weigh the pros and cons of top schools vs mediocre schools in factors such as financial aid, graduation rates, acceptance rates, and other means that might push them to apply for harder colleges.(Hoxby and Turner, 2013). Because of their lack of knowledge on the benefits of prestigious schools, they see no reason to apply there and have their children go to local universities that they may be more familiar with given the proximity.[5]

Given the clear difference in lifestyle between financially stable students and students that are not so fortunate, they tend to form different opinions and attitudes regarding their academic readiness. A study made by Jacqueline King took 900 seniors with 300 of them being a part of families earning under twenty grand a year. She took into account multiple factors including but not limited to, academic intensity, course rigor, school rigor, parents' education, and others. Her findings suggested that low-income students and their educational experiences do not align with those who commonly attend full four-year programs. (King, 1996).[6] This represents how availability bias can affect not only how ready they are to apply to top colleges with the tools around them, but also how ready they feel and their mindset regarding it, which is arguably just as important, if not more when deciding whether or not to apply.

To help overcome a cognitive function like the availability bias is no easy feat. However, today's society in particular is primed for this particular purpose. With the rapid rise of the internet and its subsequent implant into every aspect of our lives, information from the best, brightest and most trusted sources are more accessible than ever. Every year, technology and its ease of access are being turned from a luxury into a necessity, making it easier to get free information online. There are other public institutions that have internet access such as libraries that can also help in the fight to gain the knowledge necessary to put disadvantaged students on the same playing field as wealthy ones. What needs to happen for change is a mindset switch that will allow kids to gain information outside of their loved ones and look to people who are more fit for answering their needs in terms of college admissions. The most practical and affordable way for this to happen is through the internet, and more specifically universities must make an

[4] Public School Counselors can be expected to devote large amounts of time to other personal or school related problems outside of college according to the NCES

[5] This idea I formed goes in part with the finding above that is part of a hypothesis that Caroline Hoxby and Sarah Turner made about low income students and their circumstances which include parents effect on their children

[6] Observational Study was performed in 1995 to see the lifestyles of those who decide to go to college or not, however, the same reasons can be applied when learning why low income students do not apply to the best universities

effort to reach out to underprivileged students through alumni from similar backgrounds. This way they can actually have someone that has gone through a similar experience helping them out in a way that no family member could, which is with first-hand experience. Colleges should set up a website where students and their families can have Zoom meetings or calls with these alumni where they can discuss what they should do and how they should go about their journey, much like the alumni did themselves.

Section 2: Status Quo Bias

Status Quo Bias is a representation of the fear of change, something that humans have struggled to let go fight and have still not overcome. After all, neuroscientists have discovered and researched that change and uncertainty for the future give the same response as when you do something incorrectly. (Mautz, 2017)[7] This shows the inherent discomfort that comes from doing things differently than from what one is used to, and on a bigger scale, it is that much more intense. It is human nature to want to follow a routine as well as following the people around oneself, with the common example being one's parents and mentors. With these people most often being part of the same demographic as oneself, disadvantaged students often try to stay in the same lane as the people around them due to ease and convenience. Human innovation at its most fundamental level is making life more convenient.

In regards to disadvantaged students and college applications, status quo bias can have a severe impact on their decisions. A disadvantaged student can be considered disadvantaged for a number of reasons. They can come from a low-income household and/or be a part of a family that has never had a person attend college, let alone a prestigious top university. To jump from their situation to an environment like one at Harvard can be a really big step that many families are not willing to take for their children. That is why many students from lower-income families can be pressured to or believe that it is for the best to follow in their parents' footsteps and have a life outside of education. A girl named Claire Lucas, who comes from an area in Britain where many of her friends dropped school to work at a factory and her parents never went to college, decided to apply to Oxford. (Davis, 2010). Only after she stepped outside of her comfort zone and what was normal for her, was she able to experience a new world where she learned the differences between the working class and posh universities as well as reached her full potential, as an academic that can help her neighborhood.[8] When looking at multiple studies and conducting experiments regarding the human brain's reaction to the status quo and its change, researchers found that the dynamics of a specific prefrontal basal in the brain is the part that

[7] Multiple studies and philosophers have stated that it is human nature to fear change and the statement regarding neuroscience research was pulled from the following essay:
https://www.inc.com/scott-mautz/science-says-this-is-why-you-fear-change-and-what-to-do-about-it.html

[8] This is an anecdote that represents the status quo bias and how abandoning it can positively affect a person and their life going forward as well as issues that they are passionate about. In Lucas' case, the divide between the working class and the elite. Learn more about her story here:
https://www.opinionpanel.co.uk/clientUpload/pdf/Working-classrevolutionnotreachingposhunis.pdf

rejects staticness and promotes change[9], again showing the positives that come with venturing out and setting new horizons for oneself.(Fleming, Thomas, and Dolan, 2010).

Socioeconomics is a big part of selective schools, and a parent's prestige in terms of where they went to college as well as their occupation can play a big part in whether or not their child attends a top college. A 2002 study shows that only 3% of students at the most prestigious of colleges were from the lowest socio-economic backgrounds, (ie: disadvantaged families). (Delisle and Cooper, 2018). This can be attributed to a number of factors with one of them being status quo bias and the reluctance of people to move out of one's comfort zone. It is no secret that the top colleges have generous financial aid packages, so the reasoning behind this must be that parents are uncomfortable with sending their kids to institutions that they may feel as foreign to them.[10] Due to this, there is clear underrepresentation of lower-income families in top schools, as a byproduct of the effects status quo bias has on the students.

After noting the clear connection between status quo bias and the measly 8% of disadvantaged students that apply to top universities in the same way wealthy students do[11], we must find out how to prevent such an occurrence from happening so that the problem can be erased for the foreseeable future. (Gorman, 2013) In regards to college applications, status quo bias is all about firsts. In many cases, these kids are the first to apply to a top college and maybe even first to apply to any college and that can be intimidating. The best way to approach these fears is to show them that there is no cost of trying and there can be great success if one does. There have already been steps taken such as waiving admission cost but more can be done. For example, colleges should go out of their way to explain the benefits that come with not only a degree from college, but one from a prestigious university. This could be done by showing data, of the salaries, status, and futures of the kids who attend their institutions by running ads on television with the massive endowment that the top schools have. Basically, going out of their way and being proactive in showing all the reasons why people from disadvantaged backgrounds should attend their school will help bring diversity and a new batch of people from all socioeconomic backgrounds into the same playing field for future success.

Section 3: The Anchoring Effect

The anchoring effect is when people get hung up over certain quotes, ideas, phrases, and statistics that can be misleading, all because it is very alarming and it is the first piece of information a person sees about the topic. When comparing it to the other heuristics covered, it is significantly more subtle. An example of this is the myth that people need to drink 8 glasses of

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[9] Multiple experiments using participants in tests such as the line judgement game and others were used to support this claim. For more information on all the experiments, consider reading their full findings. https://www.pnas.org/content/107/13/6005

[10] The point about generous financial aid packages is from Caroline Hoxby and Sarah Turner's research paper when she pointed out that many selective unis have better packages than lower tier schools for low income families.

[11] Linda Gorman created a summarized version of the Caroline Hoxby paper where she pointed out the statistic regarding the 8% of poor students applying the same way rich ones do. I couldn't find the year that she published but I have a link to her paper https://www.nber.org/digest/may13/hidden-supply-high-achieving-low-income-students .

water a day.[12] This piece of misinformation was spread by a weight loss program promoting healthy diets, but given that it is a clear number that people can follow, many started treating it like it was actual health advice from a trusted source. This is far from the case, considering drinking water is very subjective and people need to drink only when they are thirsty. (Schimpf, 2016). This is all to show the dangers of the anchoring effect and how it uses people's quick minds and short attention spans to latch on to an idea that they won't forget, not due to its factuality, but it's captivation instead. My interpretation of the anchoring effect is when people see a captivating statistic, whether for good or bad, they will be "anchored" by it and hold on to that idea without looking further into its accuracy.

There is a certain aura that surrounds top colleges and the prestige that comes with it. As it is held in high regard, there is a clear demand from parents across the world to have their child attend one of the top institutions. Inevitably, as more and more kids apply hoping to get a seat, the admission rates go lower and lower. Not to mention the astronomically high tuition rates that force people to go into debt to cover. With that, colleges can and are oftentimes defined by two things. The first is the admission rate as it is proof to parents and kids about how competitive a school is and, in turn, its academic quality. The second is tuition as if it is unaffordable then they probably should not go to the school.[13] (Youngblood, 2015). Because of things like this, the most envied schools have very low admission percentages and because they have great resources, a very high price tag as well. In regards to disadvantaged students, parents and kids from low-income backgrounds with less resources can also get anchored by these numbers and will shy away from them. This can be attributed to a number of reasons including them thinking they cannot afford the school, or them thinking it is not worth their time as they will never get in.[14] This also links back to our first heuristic, the availability bias, as they do not have the right information as they have no one around them that understands what exactly they are going through.

More on that, multiple studies on the anchoring effect and its relation to applications were done by reputable sources. Nicholas Bowman and Micheal Bastedo conducted an experiment on the anchoring effect and how it affected the university rankings of the world and their reputation.[15] They found that of the first three years of data, the first year's data was the most important regarding the reputation of the school. This basically means that the reputation of the school was decided based on the first rankings that came out, rather than the annually updated ones. (Bowman and Bastedo, 2011). This is clearly intertwined with the Anchoring effect and the idea that people take the first piece of information they see and run with it without accounting for

[12] According to Doctor Megan Schimpf at Michigan Health, 8 glasses of water is a myth and lacks any real evidence from any established research paper or noteworthy doctor.
https://healthblog.uofmhealth.org/womens-health/myth-busting-no-more-8-glasses-a-day

[13] The article shows that a majority of parents look for both a first rate academic experience which often can be seen with how competitive a school is as well as the affordability.

[14] We know that there are financial aid packages as well as the fact that selective colleges try to accept people from all socio-economic backgrounds, but as people who do not know much about prestigious colleges, they often will not know about this and believe it isn't worth it.

[15] They examined their data using the Times Higher Education Supplement (THES) world rankings for its first three years.

other factors. This can also be connected to disadvantaged students and their parents as it shows how when looking at colleges and schools, and subsequently, rankings, they can be heavily influenced and intimidated by rankings of schools and their admissions rates, turning them away from applying.

As previously noted, holding on to the first piece of information obtained is easy to do and hard to stop. After all, it's easier to think that you need to drink 8 glasses of water a day to be healthy, even if it isn't true. In the same way, it is easy to say that you will never get into that college or you can never handle the financial burden, and then not apply without even looking into it. One practical solution to this is if public schools in these lower-income communities make an effort to educate their students on universities and colleges so that their first experience with the topic is from a credible source. This can be implemented by having universities invest in these lower-income communities and have them hold info sessions in public centers at no cost to the families attending. This would assure that the parents and students are not swayed by anchoring bias as they are learning long before they have to face the issue when the kids are seniors applying to colleges and universities. This way, colleges would also benefit as they wouldn't have to worry about missing out on top students due to anchoring and can focus on their applications.

Conclusion

With the noticeably low amount of low-income students attending prestigious universities, we start to question what these colleges are doing wrong when trying to attract people from all socio-economic backgrounds. The answer, however, is they are doing enough. Several different papers written by reputable researchers have concluded that the most selective universities have done some of the best work for poorer students.[16] Caroline Hoxby has found that many of the situations regarding low-income students and their worries are not uniform throughout their schools and can be treated as unique, isolated issues(Hoxby and Turner, 2013). Furthermore, a study done by Jason D. Delisle and Preston Cooper has concluded that the situation regarding affordability at the most prestigious of colleges is in good shape and they do not necessarily need to do more than they are already doing. (Delisle and Cooper, 2018). This includes affirmative action, financial aid packages, and more. This makes it clear that the explanation behind why top students do not apply to these top colleges has less to do with the institutions themselves, and more to do with their own personal heuristics on the matter.

[16] Both the research papers done by Jason D. Deslisle and Preston Cooper as well as Caroline Hoxby and Sarah Turner respectively both back the claim with their conclusions matching the statement.

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Social Inequality in Korea and How It is Represented in Parasite and Squid Game By Hakyung Song

Abstract

Twenty-first-century Korean society has experienced severe repercussions from rapid economic development based on neoliberal capitalism. This has manifested as increased societal polarization, fierce competition, and loss of humanity. In this paper, I compare and analyse two similar yet distinct media that enthralled audiences around the world: the film Parasite (2019) directed by Bong Joon-ho, and the Netflix drama series Squid Game (2021) directed by Hwang Dong-Hyuk. I aim to explore how these works, which serve as miniaturized fables of Korean society, expose the negative side of Korean capitalism. I examine the polarization of wealth depicted in the two media and focus on the various problems of Korean society, particularly the socioeconomic inequality that appears as ridicule, hatred, and corresponding violence. In addition, I compare the authors' intentions by analysing the different methods the characters used to resolve the issues stemming from such social polarization. Finally, by reflecting on contemporary Korean society and how the theme of human dignity is dealt with in these works, I evaluate their messages of hope.

Keywords: Competition, Contemporary, Human dignity, Korea, Korean film and television, Korean media, Korean society, Loss of humanity, Neoliberal capitalism, Parasite,

Introduction

Hallyu, which refers to the trend of Korean cultural content that was originally noted in the early 2000s, is currently spreading across the world. Owing to the popularity of Korean dramas, films, and music, OTT platforms are experiencing a surge in demand for Korean content. These works are attracting attention for various reasons, such as outstanding work performance, visual appeal, technology, quality of the direction, and acting. Among these, director Bong Joon-ho's *Parasite* (the first Asian film to win the Best Picture and Best Director awards at the Academy Awards) and the sensational series *Squid Game* (which topped Netflix's global ratings) are quintessential pieces of popular Korean content. However, these two works have another aspect in common: namely, they show the social problems that Korean society is experiencing from a critical perspective. Korean society has achieved rapid growth at a tremendous speed after the Korean War, and the unlimited competition of free economics and the markedly rapid development of a capital-centred society have facilitated considerable economic development. However, various social side effects have also emerged. By examining the aforementioned two works, which explore these problems, a better understanding of Korean society can be obtained. In addition to the wealth gap, infinite competition and the resulting loss of humanity penetrate both works. In this paper, these two works' portrayal of the polarization of wealth as well as their overall messages are examined.

Background: Twenty-First Century Korean Society

The neo-liberalism theory is based on the claim that the best results for the economy are caused by free competition among markets and industries. This theory had removed several policies that limited free economic and business activities. In particular, it required abolishing policies related to the employment sector and government interference. Moreover, the theory posits that the privatisation of industries should be promoted instead of making public goods. However, this theory has also been criticised because it causes a vicious cycle of poverty and does not solve the problems of high unemployment and low growth rate of the economy (Jung, 2001).

The manner in which the poor perceive self-identity fascinates the audience. The extremely polarized depictions of the poor and the rich, in which the poor are evil and the rich are good, engender considerable interest. For example, in *Parasite*, a family in the lower class is portrayed as being unemployed, parasitising a wealthy family, and lacking independence. The wealthy family, in contrast, is portrayed as knowledgeable, classy, and kind to everyone. This contrast shows how the poor family, whose perspective the movie adopts, views itself and the wealthy family. In *Squid Game*, people who lack economic power and social status participate in a dangerous game for a chance to drastically change their lives. This series garnered favourable criticism by making a fascinating storyline focusing on present-day Korean society's problems. This series handles various relevant issues, including sexism, North Korean defectors, and migrant workers.

The Polarization of Wealth and Its Depiction in These Two Media

In *Parasite*, as the Kim family lives in a semi-basement house (i.e. a house that is half at the ground level and half underground), when the camera is showing the window from indoors, the ground level is slightly higher than their floor; thus, the camera angle is slightly tilted upwards. The members of the family are unable to see people from eye level through the window, and they are looked down upon by pedestrians (Filmmakers Academy, 2022). When a drunken man seeks a place for public urination, he decides to do it on their window, which implies he does not expect someone to live there, as people often choose a dark or even filthy alleyway away from people for urination. This scene further suggests how poor people are treated in real society. Urinating on another person's house is highly insulting behaviour. Such behaviour is also hard to imagine. Thus, *Parasite* shows that this poor family's house is uninhabitable. This suggests that the reality that poor people have to live in uninhabitable places is absurd. Moreover, the situation in which poor people are ignored even by a drunk person highlights the social status of poor people.

The Kim family's body odour is caused by their living conditions, which include a lack of light as well as wet, humid conditions. These conditions make the house mouldy, and the people living there acquire the same odour. Furthermore, they are unable to disguise this smell. This shows how people are unable to recognise their social status without other people, such as wealthy families. Thus, *Parasite* uses body odour to depict two different statuses in society: poor

and wealthy. The film never mentions the wealthy family's smell, but it constantly shows that the smell of the Kim family cannot change or be recognised by the family members, while people of higher status can smell them easily. These factors show that the poor in Korea are unchangeable and unable to hide and that wealthy people feel hostility towards them. The ending of the film shows Bong's pessimistic perspective: namely, it is hard to bridge the gap between the poor and the wealthy. Furthermore, the smell causes Kim, the head of the poor family, to murder Park, the head of the wealthy family. When Park covers his nose because of Kim's smell, the latter feels insulted and angry; as a result, he assaults Park. Prior to this final scene, there are several scenes where a wealthy family member covers their nose because of the poor family members' odour. Kim thinks that every person is the same even though they have different social statuses. However, Park and the other wealthy family members' behaviour leads to social alienation and destroys Kim's aforementioned belief. This elicits Kim's anger, which he expresses by murdering Park. This scene emphasises how socialism is alienating poor people from society and how it leads to unpleasant consequences in the future.

Similarly, *Squid Game* shows a vertical hierarchical society using the participants in the game and the VIP audience watching the game. It shows camera technology in which the VIPs are watching the participants from above. For example, in one of the games, in which the players have to cross a transparent bridge, the VIPs are watching through the screen. The cameras recording the players are located at the top. Thus, the VIPs can see players from the top. These camera angles show a vertical hierarchical structure like in *Parasite*. While the participants engage in the game desperately, the VIPs watch and enjoy these games on video. They do not feel sad about the death of the participants; instead, they applaud when the participants die in thrilling ways. These behaviours show that rich people have turned people who need money into spectacles for their amusement. Several other films also depict wealthy people in a similar manner (Lee, 2021). In *Gladiator* (2000) and *The Hunger Games* (2012–2015), people watch the fights between the participants and are enthusiastic about others' misery. The participants in those films are also treated as sources of entertainment. However, there is a difference between these two movies and *Squid Game*. In *The Hunger Games*, the victorious participants are promised a life of luxury in the Capitol. In contrast, in *Squid Game*, the winner gets 38.16 million dollars. This shows that money is the most important factor in present-day society. In addition, several lines in the series, such as 'If you can't hold on, you'll drop out', reveal the serious issues pervading present-day society. It emphasises the economic differences between the wealthy and the poor in modern society by highlighting the economic problems faced by many; for instance, several people are unable to withstand rising housing prices and inflation.

Squid Game uses visual elements to show the gap between poor and wealthy people. In the series, the participants of the game, who are poor and have low social status, are made to wear the same simple clothes. In contrast, the VIPs, who are very wealthy, wear distinct luxurious clothes and golden masks. This difference emphasises the contrast between the wealthy and the poor. It shows that wealthy people have considerably greater freedom of choice in society. Moreover, the VIPs wearing golden masks is a reference to certain facets of Korean

society and culture. In Korean society, people call wealthy people, especially those who are wealthy because of their family, gold spoons. Thus, wearing a golden mask highlights their economic status via a cultural reference.

In contrast to *Parasite*, *Squid Game* portrays the wealthy VIPs as villains, while the poor participants are portrayed as victims. This setting helps the audience adopt a positive perspective towards the participants. In addition, it arouses sympathy, causing the audience to support the poor people rather than the VIPs. This is also connected to Korean society. There is a common belief, the veracity of which remains uncertain, that wealthy people are exploiting others and growing wealthy through illegal means. Thus, this shows people's negative perspective towards rich people in contemporary society.

The Possibility of Upward Social Mobility

Parasite and *Squid Game* adopt different stances towards upward mobility in economic and social status. *Parasite* has scenes that show attainable success, such as using semi-basement housing (Yonhapnews, 2019a). However, in the end, it emphasises that attaining a higher economic status is impossible. In the ending, there is a scene where Ki-woo succeeds and moves to the house where the wealthy family lived to escape his father. However, it is later shown that this was all imagined by Ki-woo. Thus, the movie shows the poor family's delusions, emphasising that moving upwards in society is impossible (Kim, 2020).

In contrast, *Squid Game* shows that a change in economic and social status is possible. The main character, Gi-hun, participates in the game with no money and the lowest social status, but he wins the game and gets 38.16 million dollars. Thus, the series' message seems to be that people can change their status if they try hard. However, it also shows that this process is extremely difficult, as only one participant wins the prize and escapes the game. Even though various other participants try as hard as Gi-hun, they could not win. This emphasises how hard it is for people to change their economic status in contemporary society.

The Message of Human Dignity

Parasite reflects the reality of present-day society, where the gap between the rich and the poor is evident. The despair and anger of ordinary working-class people who cannot afford their own homes, no matter how hard they try, reflects a time when it may be necessary to survive parasitically in a society (Yonhapnews, 2019b).

The film depicts the poor family as not possessing any morality or ethics; they boast of the success they gain through deception and hypocrisy. This reflects the social achievements that are difficult to attain through normal means, even for people who attend the best universities or work hard. The hierarchical relationships between classes, illustrated by the unattainable staircase or the unattainable house portrayed in the film, represent an absolute power that cannot be reached even if the people involved have similar abilities. This can be seen as reflecting the reality of present-day society. In essence, to survive in a social reality that does not seem to

improve over time, the Kim family chooses to give up their morality and parasitise the wealthy upper class by any means necessary.

Similarly, *Squid Game* depicts people who are economically unsuccessful but are forced to participate in fierce competition in a death game designed by the uber-rich. There is no hope, and thus, they have no choice but to risk their lives. In the past, there was hope that, if you worked hard, you could live well and reach the top. However, phrases like 'Hell Joseon (former Korean dynasty)' or 'This life is a failure' have become popular, indicating a society that has lost hope.

Both the film and the series portray how contemporary society is structured, with a focus on how poor people can better their situation and raise their status.

Conclusion

Both *Parasite* and *Squid Game* depict contemporary social issues, namely the gap existing in people's social and economic status in the world, including Korea. They use various storylines, camera work, and cinematography to convey their messages to the audience. Furthermore, they address the themes of human dignity and morality in the face of survival and pride. Both works have attracted considerable attention and gained a reputation because they succeed in depicting the problems inherent in real Korean society in addition to their interesting plotlines. However, greater attention should be paid to the real purpose of these works rather than their plots. These two works prompt the audience to contemplate what action should be taken to improve contemporary society's problems. By analysing these two media, I have examined contemporary society through the lenses of social economic theories such as capitalism and polarization. Regardless of their popularity, both works contain deeper insights that warrant further examination. The social and economic issues presented in them are serious and important problems that not only Korean society but also the entire world should focus on and resolve.

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Freedom House Analysis for Argentina By YuQi Feng

Freedom House Scores are a fascinating measure used to evaluate the level of democracy achieved by countries throughout the world.

The two most significant factors that go into Freedom House ratings are Political Rights (PR)" and "Civil Liberty (CL)." The Political Rights score reflects the ability of individuals and groups to participate in the political process and to have a voice in the government. Examples of political rights include the right to vote, the right to run for office, the freedom of association and assembly, and the right to access information.

The Civil Liberty score reflects the freedoms and protections that individuals have from government interference in their personal lives. Examples of civil liberties include freedom of speech, freedom of religion, freedom of the press, the right to a fair trial, and protection against arbitrary arrest or detention.)

Obviously, the Freedom House Scores vary a lot between countries due to the different attitudes and positions of their leaders. More interestingly, Freedom House scores can fluctuate dramatically within a single country due to political changes. Argentina offers a stark example of such fluctuations between 1972 and 2021, as seen in the chart below, and this piece discusses the causes and consequences of such political changes.

As the chart reflects, there were the major changes in Argentina's Freedom House scores in the 1970s and 1980s, but then -- after another fluctuation in the early 2000s -- the democratic level in Argentina became low and stable. This pattern closely corresponds to changes in political power in Argentina between 1972 and 2021.

1973: The Election of Juan Peron

In the 1973 elections, the populist politician Juan Perón was elected president, and took steps to expand political participation. Perón lifted the ban on opposition parties that had been in place during the military dictatorship that ruled before 1973, allowing for greater political pluralism and competition. He also convened a national assembly to draft a new constitution, which included provisions for greater civil liberties, such as freedom of expression and association. Further, he strengthened labor protections and increased union representation.

However, his policies added pressure to the country's economic status, which laid the groundwork for the future decline of democracy.

1976: Rule by Military Regime

The gains in democracy made during this period were quickly erased by the military regime in **1976** that followed. The military government ruled with an iron fist, suppressing political opposition, and curtailing civil liberties. Generally, the regime added more restriction, and weakened protections, of Argentinian democracy.

1981: A New President

In **1981**, the military junta that had been in power since 1976 began to experience internal divisions, with some members advocating for a transition to civilian rule. This led to the appointment of General Leopoldo Galtieri as the new president of Argentina in December 1981. **In March 1982**, he also relaxed some of the restrictions on the press and political opposition. As a typical example, he lifted the ban on newspapers and allowed them to report information related to military court. - However, his contribution towards democracy was limited since his actions were considered a passive response towards mounting international condemnation. In essence, his government remained a military regime.

1982: Falklands War

The outbreak of the Falklands War in April 1982 had a significant impact on Argentina's democracy. The military government decided to invade the Falkland Islands but were defeated, an event that undermined its legitimacy and led to widespread calls for a return to civilian rule.

1983: Democratic Election

In December 1983(, Argentina held its first democratic elections in nearly a decade, and Raúl Alfonsine was elected president. The new government took steps to restore political freedoms and civil liberties, including repealing press censorship and allowing freedom of expression. It also reformed elections by introducing a secret ballot and lowering the voting age to 18, which increased political participation.

However, as in the previous case of Juan Peron's rule, the economic policies implemented proved unsustainable, and led to hyperinflation in the late 1980s. Such fluctuation resulted in political instability and led democracy to decline.

1999: Fernando de la Rúa Presidency

In 1999, Fernando de la Rúa was elected president, running on a platform of economic and political reform. His government implemented several measures aimed at strengthening democracy, including reforms to the judiciary, the establishment of an anti-corruption agency, and measures to increase government transparency and accountability. His government also established a new agency to investigate past human rights abuses issues, which further contributed to the rise in civil liberty.

2001: Political and Economic Turmoil

The political instability and economic turmoil of **2001** had a profound impact on Argentina's democracy. Citizens were very dissatisfied with the government. They went on parades to protest against the government's weak economic policies and corruption. Such social dissatisfaction finally led to the resignation of President Fernando de la Rúa and his whole government. The government's response to the crisis was marked by increasing authoritarianism

and a crackdown on civil liberties, as it attempted to maintain control in the face of widespread social unrest. As you can imagine, this further raised the PR and CL figures.

2003: Nestor Kirchner Presidency

Finally, in **2003**, Néstor Kirchner was elected president, and his government launched a series of reforms aimed at strengthening democracy and promoting social justice. One of the most significant reforms was the establishment of the National Institute Against Discrimination, Xenophobia and Racism, which aimed to promote human rights and combat discrimination against marginalized groups in Argentina.

What Argentina's Freedom House Scores Teach Us About About Democracy

One of the main reasons for Argentina's decline in democracy is the rule of military regimes, while gains in democracy often follow the leadership of Populist or other democratic parties. As to what causes shifts between ruling parties, the suppression on democratic rights by the military regime causes dissatisfaction among voters, while the rule of democratic parties is often unpopular because their policies create an overwhelming burden on the economy.

Additionally, Argentina's history teaches us that fluctuations in democracy scores are consistently associated with policies including: press censorship, voting rights, free election, protection of human rights, and a sustainable economy.

Observing the fluctuations in Freedom House scores in Argentina allows us to not only understand the impact of different governments – and government policies – on democracy in Argentina but allows us to better understand the factors that might undermine democracy in other countries as well.

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A Comparative Analysis of Elizabeth I of England and Catherine the Great of Russia: Empowering and Extending National Power By Madeline Xie

Abstract

Throughout history, female rulers have been a rarity, with only a handful emerging amidst countless male leaders. This paper aims to explore and compare the reigns of two powerful female monarchs, Catherine the Great and Elizabeth I, to shed light on their strategies for enhancing and lengthening the national power of their respective states. In a patriarchal world, understanding the accomplishments and challenges faced by these remarkable queens provides valuable insights into female leadership and the requirements for advancing a nation.

Importance of the Topic

Examining female rulers and their contributions to their nations is of great significance as it offers valuable knowledge on the historical roles and capabilities of women in positions of power. By delving into the reigns of Catherine the Great and Elizabeth I, we can gain insights into various leadership styles that led to their empowerment and garnering of respect. While both queens achieved remarkable success, this paper will argue that Elizabeth I's reign was slightly more advanced and successful than Catherine the Great's.

Methodology

This paper will employ a comparative approach to analyze the actions and decisions of Catherine the Great and Elizabeth I in a pragmatic manner. Moral considerations will not be taken into account for the sake of objectivity, clarity, and fairness. Recognizing the negative aspects of actions, such as the exploitation of serfs and invasions of freedom, the analysis will focus on the pragmatic outcomes and implications of their decisions.

Disclaimer

It is essential to acknowledge that geographical, cultural, and temporal differences may have influenced the queens' decisions. While recognizing these factors as potential critical elements, this paper will primarily concentrate on their pragmatic choices and their impact on national power.

In conclusion, by undertaking a comprehensive study of Catherine the Great and Elizabeth I, we aim to shed light on the capabilities and challenges faced by female rulers in their quest for enhancing and lengthening national power. While recognizing their unique accomplishments, we will argue that Elizabeth I's reign stands out as slightly more successful due to her advanced leadership approach.

Background

During Catherine the Great's reign (1762-1796), Russia experienced significant territorial expansion and economic growth, solidifying its position as a major European power. Catherine's

policies and military campaigns played a crucial role in the transformation of Russia during this period.

One of the major territorial expansions occurred through the Russo-Turkish Wars of 1768 and 1787. These wars were fought against the Ottoman Empire, and through a series of victories, Russia gained control over significant territories in the Black Sea region and the Caucasus, expanding its influence in Eastern Europe and the Middle East. In 1787, Russia also engaged in the Russo-Swedish War, which resulted in the annexation of territories along the Baltic Sea, further enhancing Russia's access to important trade routes and maritime power. Additionally, Catherine oversaw the partition of Poland on three occasions. The partitions of Poland in 1772, 1789, and 1795 allowed Russia, along with Prussia and Austria, to acquire substantial portions of Polish territory, effectively erasing Poland from the map for over a century. These partitions not only expanded Russia's borders but also weakened one of its neighboring powers.

Catherine the Great's reign also saw significant economic advancements. She implemented a series of economic reforms aimed at modernizing and industrializing Russia. These reforms encouraged foreign investments, promoted trade, and boosted agricultural production, leading to economic prosperity and growth.

Furthermore, Catherine was a patron of the arts, literature, and education. She founded numerous cultural institutions and supported the works of prominent writers, philosophers, and artists, contributing to a flourishing cultural scene in Russia.

Overall, Catherine the Great's reign was marked by ambitious territorial expansion and economic development, elevating Russia to a prominent position among European powers. Her legacy as a powerful and influential ruler is still remembered today, and her reign is considered a crucial period in Russian history.

Queen Elizabeth I played a pivotal role in shaping the success of the British Empire during her reign from 1558 to 1603. Her rule and policies had a profound impact on England's overseas expansion and the establishment of the British Empire. Like Catherine the Great, Elizabeth pursued a flexible foreign policy that aimed to expand England's territorial influence and secure valuable overseas possessions. She supported exploratory voyages and encouraged private investors to finance these expeditions, leading to the discovery and colonization of new territories. One of the most famous examples of her support for exploration was the sponsorship of Sir Francis Drake's circumnavigation of the globe from 1577 to 1580.

Under Elizabeth's rule, England successfully defeated the Spanish Armada in 1588, which not only secured England's position as a naval power but also dealt a significant blow to the powerful Spanish Empire. This victory further facilitated England's expansion into the New World, where it established colonies in North America and the Caribbean. Elizabeth's policies also fostered economic growth and prosperity in England, laying the foundation for its future dominance in global trade. She supported the growth of trade and industry, leading to the rise of powerful merchant companies like the East India Company and the Hudson's Bay Company, which played a crucial role in England's overseas ventures.

Moreover, Elizabeth's reign marked a golden age of English literature, theater, and arts. Playwrights like William Shakespeare flourished during this period, contributing to the cultural influence of England throughout its expanding empire. Elizabeth's reign saw England forge key alliances with other European powers, including the Dutch Republic. These alliances strengthened England's position in international politics and enabled further expansion of its overseas territories. Queen Elizabeth I's rule and policies laid the groundwork for the future growth and success of the British Empire. Her strategic vision, support for exploration, promotion of trade, and cultural patronage all played essential roles in elevating England to become the empire on which the sun never sets. The legacy of her reign is still evident in the historical and cultural influence of the British Empire and its lasting impact on the world.

Central Thesis

Although Catherine the Great significantly expanded Russian territory and westernized Russia, Queen Elizabeth had a greater impact on a global scale because her policies were a turning point of England and created a more advanced version of England with domestic peace, better economy through exploration, trade, and the establishment of English nationalism. Elizabeth's reign also oversaw an increase of English cultural influence throughout the world through the renaissance. Elizabeth was, therefore, a more successful ruler than Catherine due to her advancement of England's national power. In short, Elizabeth's vision went far beyond her own era. She understood that people who change history should not adapt but initiate change. Therefore Elizabeth's institutional innovation set an exceptional foundation for English power even after her regime ended. In contrast, while Catherine's rule in Russia witnessed notable advancements, the nation's subsequent political state remained unstable and on the brink of revolution even immediately after her reign. Therefore, Elizabeth emerges as the more successful ruler due to her profound impact on England's national power and her ability to initiate transformative change.

Context: Under Previous Rulers

Europe in the 16th century witnessed a massive expansion of economic output, and a more tightly connected world through trade, exploration, and the rise of imperialism[17]. With increasing naval technologies, powerful European countries sponsored expeditions to seek resources in different parts of the world. In this era of mercantilism, the economic system was seen as a zero-sum game where mutual gain was viewed as impossible. Emphasis was placed on accumulating resources and controlling trades. The increasing interactions of European countries hand in hand with nationalist policies, soon brought disputes of interest.

Prior to Elizabeth's rule, England was very divided domestically and had nothing both economically nor militarily that could compete with other European powers like Spain and Portugal[18]. England was divided domestically caused by the dispute over religion in the early

[17]https://www.britannica.com/topic/history-of-Europe/The-emergence-of-modern-Europe-1500-1648
[18] https://localhistories.org/a-history-of-england-in-the-16th-./

16th century. The 'Act of Supremacy' initiated by Henry the VIII led to the separation from the Catholic Church, and the formation of the Church of England. However, after King Henry died, his daughters, Queen Mary's regime brought England back to Catholicism along with persecuting Protestants.

In the 18th century, Russia was a vast and diverse empire, stretching across Eastern Europe and Asia. Under the rule of Peter the Great, Russia underwent significant modernization and territorial expansion. Peter's centralized monarchy allowed him to consolidate power and undertake ambitious reforms to transform Russia into a more European-style nation. However, prior to Catherine's rule, Russia faced a period of turmoil and decline after the death of Peter the Great in 1725. His successors were often incompetent, leading to administrative and economic chaos, as well as an empty treasury. Corrupt officials under the Tsar's rule were rampant, extorting the people and causing widespread resentment among the peasants, leading to various uprisings and disturbances across the country. One of Peter III's most significant mistakes was his decision to withdraw Russia from the Seven Years' War, a conflict that had been ongoing since 1756. This move was deeply unpopular among the military and nobility, who saw it as a betrayal of Russia's allies and a weakening of the country's position on the international stage. Peter III's strong admiration for Prussia and his open admiration for Frederick the Great, the King of Prussia, only added to the discontent among the Russian nobility and military. This pro-Prussian stance was seen as a betrayal of traditional Russian alliances and interests, further eroding support for his rule.

These different power dynamics and historical backgrounds shaped the challenges and opportunities that Elizabeth and Catherine faced during their reigns. Elizabeth had to navigate religious tensions and assert England's standing in a rapidly changing Europe dominated by mercantilism and national rivalries. Catherine, inheriting a powerful and expansive Russia, sought to maintain and strengthen its position as a major European power while implementing reforms and cultural advancements.

Secure the Regime

Due to this set of history, In November 1558, when Elizabeth I succeeded at age 25 after her half sister, Mary's death, she faced a decentralized country filled by hatred after unstable religions. As a Protestant, Elizabeth faced constant threats from catholics, which was a huge obstacle to legitimize her rule. The Catholic rebellion in 1569 tried to replace Elizabeth with Mary, Queen of Scots deeply showed the instability for her. Thus, when Elizabeth first tasted her power, she immediately put her effort into restoring the unity of England. She understood that religious dispute could only harm her as a Protestant ruler, and that religious disputes only cause problems within England that prevent it from further economic and political development. To unify, stabilize England, and also to legitimize her power, Elizabeth imposed the Religious Settlement in 1559, also known as the 'middle way'[19]. She established Anglicanism that combined Protestant doctrine and Catholic rituals. In which she hoped to ease the anger of both

[19] https://www.bbc.co.uk/bitesize/guides/z8qpjty/revision/2

sides. The Religious Settlement revealed her stance on religion that differed from her former rulers. Compared with Elizabeth's former rulers, she was way more tolerant, and her visions were far beyond religious conflicts. Elizabeth's act certainly united English national identity. *The Expansion of England*, written in 1883 by John Robert Sealey, revealed in this book that under the rule of Queen Elizabeth I, English people turned into a nation that's mercantile and seafaring[20]. By using this legal process, Elizabeth made herself the Supreme Governor of the Church of England that continued to place monarchy power over religion. However, an Protestant led England caused hostility from major Catholic countries, such as Spain and France. They viewed Elizabeth as illegitimate and the ambition to dethrone her rose quietly.

Catherine the Great of Russia made deliberate efforts to approach and win the favor of Queen Elizabeth I. Despite being a highly revered monarch, Queen Elizabeth saw remarkable potential in the young Catherine. Catherine actively embraced the Eastern Orthodox faith and eventually became a devout follower. Her connections with influential figures and her genuine interest in the Orthodox religion helped her gain support among key political factions. In June 1762, Catherine orchestrated a successful palace coup that resulted in her ascension to power, replacing her husband, Peter III. In her coronation declaration, she portrayed the power struggle as "the choice of the Russian people," effectively legitimizing her position as ruler. As she began her reign, Catherine was mindful of the potential for large-scale peasant uprisings and, therefore, sought to strengthen the power of the nobility over the serfs. However, at the same time, Her policies aimed to secure the economic dominance of the nobility and expand their landholdings. Catherine's rise to power was not without challenges and complexities. She skillfully navigated the Russian court and political landscape to solidify her position as Empress. Her intelligence, diplomacy, and understanding of the Russian nobility played crucial roles in her successful ascension to the throne.

Comparison

Both Queen Elizabeth I of England and Catherine the Great of Russia demonstrated a remarkably open attitude towards religion, which played a crucial role in shaping their reigns and the religious landscapes of their respective nations.

Elizabeth I's approach to religion is perhaps best characterized by her quest for religious moderation and compromise. In the tumultuous period of the English Reformation, she inherited a kingdom deeply divided between Catholics and Protestants. Recognizing the destructive consequences of religious conflicts, Elizabeth sought to establish a religious settlement that would bring stability and unity to England. Her establishment of the Church of England through the Act of Supremacy in 1559 created a media, or "middle way," between Catholicism and radical Protestantism. This allowed for a measure of religious freedom and provided a space for both Catholics and Protestants to practice their faiths, albeit under the supremacy of the monarch as the Supreme Governor of the Church.

[20]https://www.dedao.cn/share/packet?packetId=E21WxkYoZWVYJrpVtkQgt9nAOLrj04nv&state=https%253A%252F%252Fwww.dedao.cn%252Fshare%252Fpacket%253FpacketId%253DE21WxkYoZWVYJrpVtkQgt9nAOLrj04nv

Elizabeth's approach to religion was pragmatic and aimed at consolidating her power while maintaining social harmony. She skillfully navigate between competing religious factions, and her policies effectively ended the religious turmoil that had plagued England for decades. Her religious settlement laid the foundation for a stable and relatively peaceful religious landscape in England, which endured for many years after her reign.

On the other hand, Catherine the Great embraced a different religious path when she converted to Eastern Orthodox Christianity. Born as a German princess, Catherine married into the Russian imperial family and eventually ascended to the throne as Empress. Recognizing the deeply ingrained influence of the Orthodox Church in Russian society, Catherine took the momentous step of converting to the faith. This move was not only a personal expression of faith but also a strategic political decision to gain the support and acceptance of the predominantly Orthodox population.

Catherine's conversion to Orthodox Christianity bolstered her legitimacy as a Russian ruler and strengthened her ties with the nobility and clergy. It demonstrated her willingness to embrace the cultural and religious traditions of her adopted nation, cementing her position as a rightful ruler in the eyes of her subjects. By aligning herself with the Orthodox Church, Catherine gained religious authority and respect, further consolidating her power over the vast Russian Empire.

In comparison, while both queens displayed openness to religious practices, their approaches were distinct in their context and implications. Elizabeth's pursuit of religious moderation brought stability to a religiously fractured England, allowing for coexistence and religious freedom. On the other hand, Catherine's conversion to Orthodox Christianity was a strategic move to solidify her rule and earn the loyalty of her predominantly Orthodox subjects.

Overall, the religious attitudes of Elizabeth and Catherine had significant impacts on their reigns and the societies they governed. Their open-mindedness towards religion allowed them to navigate complex religious landscapes and secure their positions as influential and successful female rulers in history.

Ruling Style: Visions and Goals

Elizabeth I and Catherine the Great, two powerful female rulers from different eras, exhibited contrasting ruling styles and visions for their respective nations.

Elizabeth’s era was famous for its *defensive* moves that could be represented by her quote: “I observe and remain silent”. Elizabeth’s foreign policy could be concluded as avoiding conflicts, avoiding forming enemies, and avoiding marriage. Along with policies advocating encouragement to explorations, and domestic policies encouraged economic growth, establishment of English national identity, and advancement of the institutional system. But under all these defensive moves, Elizabeth had great visions that went beyond her era and ambitions for England to be more advanced than others. For instance, Elizabeth saves England’s energy from harmful international disputes, but puts them in her reforms in the domestic institutional system that benefited England even long after she passed.

Unlike Elizabeth's defensive approach, Catherine pursued a more assertive and expansionist foreign policy. She sought to expand Russian territory and influence through military campaigns. Catherine's era was famous for her *aggressive* style of political moves. A successor of Peter the Great's leadership style. The Russian empress Catherine II (1729-1796), known as Catherine the Great, reigned from 1762 to 1796. She expanded the Russian Empire, improved administration, and vigorously pursued the policy of Westernization. Her reputation as an "enlightened despot," however, is not wholly supported by her deeds. She was drowned in her ambition to modernize Russia with more efficient bureaucracy, and she believed that enlightenment ideas could support her reforms on both legal and economic aspects. As a highly informed person and a good writer, Catherine believes in the essential importance of education. Catherine wrote A General Statute for the Education of the Youth of Both Sexes and published it in March 1764. This essay argued that education is the responsibility of the State[21].

Economy–Domestic Economic Policies of Elizabeth I

Before ascending to the throne, England faced a significant debt of £300,000, which placed immense pressure on Elizabeth to improve the country's economy and limited her ability to engage in costly actions like wars. This compelled her to adopt a defensive approach and prioritize maintaining peace with other nations. During her reign, Elizabeth received advice from the financier Thomas Gresham, who proposed Gresham's Law, stating that "bad money drives out good money." Gresham recommended that Elizabeth take back the undervalued pounds and reissue them as pound sterling. Although this approach carried the risk of high costs for the government and slow effects on the economy, Elizabeth embraced the advice, seeing beyond short-term challenges to envision long-term prosperity for England. She recognized that a stable pound with high credit was crucial for the nation's success.

Implementing a frugal policy that reduced unnecessary spending and focused on stabilizing the pound, Elizabeth successfully paid off all the debt within a decade. Her prudent approach not only restored confidence in the pound but also laid the foundation for its stability for the next 370 years. The British government continued to follow Elizabeth's policy, and the pound's value remained remarkably stable over three centuries.

Domestic Economic Policies of Catherine the Great

Before Catherine's regime, Russia was burdened with significant debts and financial difficulties. Like Britain, the country had accumulated substantial debts from past wars and imperial ambitions, leading to financial constraints and limited resources for economic development. Trade Restrictions: Russia's trade was subject to strict regulations and limitations imposed by the government. Foreign trade was often controlled by state monopolies, which restricted the growth of private enterprises and limited the inflow of foreign investments. During Catherine the Great's reign, she pursued various domestic economic actions to modernize and strengthen Russia's economy. Some of her notable initiatives are:

[21] https://www.bestessay.com/essays/catherine-the-great.php

1. Agricultural Reforms: She encouraged the adoption of new farming techniques and technologies, such as crop rotation and improved irrigation systems. These measures led to significant improvements in agricultural yields and helped to alleviate food shortages in some regions.
2. Industrial Development: She established state-sponsored manufacturing industries and encouraged the growth of private enterprises. Her government provided financial incentives and tax breaks to attract foreign entrepreneurs and skilled craftsmen to Russia, contributing to the expansion of industrial production.
3. Trade and Commerce: She improved transportation infrastructure, such as roads and waterways, to facilitate domestic and international trade. Additionally, she negotiated favorable trade agreements with other countries to promote the export of Russian goods and increase the flow of foreign investments.
4. Education and Enlightenment: As part of her efforts to modernize Russia, Catherine promoted education and enlightenment. She established schools, universities, and academies to provide a more educated and skilled workforce. Catherine also patronized arts, literature, and science, fostering a cultural and intellectual atmosphere that contributed to the nation's progress. She encouraged the construction of public facilities, such as hospitals, schools, and cultural institutions, to improve the overall quality of life for Russian citizens.
5. Fiscal Reforms: She introduced more efficient tax collection systems.

Foreign Economic Policies of Elizabeth I

Queen Elizabeth I pursued a more liberal form of mercantilism during her reign, deviating from previous approaches. She boldly allowed private investors to collaborate in ventures with high risk, despite opposition from those who viewed such endeavors as potentially ignominious due to their profit-driven nature and susceptibility to rivalry, fraud, and envy. Undeterred, Elizabeth's insight and courage led her to tolerate the rise of individual wealth and promote collaboration outside of government control.

Under her more liberal policies, massive British joint-stock companies emerged, founded by ambitious, devoted, and motivated investors. These companies played a significant role in English settlement in the Western Hemisphere. Unlike other colonial powers, like Spain, that maintained strict control, English colonies were largely shaped by individual initiative, fueled by the attachment to personal profits. This approach contributed to the longevity and success of English colonization, surpassing its predecessors.

Elizabeth's policies, which motivated individuals by granting them a true stake in the success of colonies, had a profound and lasting impact. Her visionary and open-minded leadership distinguished her among monarchs of her time. By fostering an environment that encouraged private investment and individual wealth accumulation, Elizabeth laid the groundwork for the development of capitalism in England, setting it on a path towards economic advancement and prosperity.

Foreign Economic Policies of Catherine the Great

Catherine the Great was dedicated to the development of Russia. During her reign, Catherine the Great of Russia (1762-1796) was determined to continue the legacy of Peter the Great's governance and propel Russia's development.

Her dedicated efforts to develop Russia's economic power and influence were exemplified by her strategic focus on the Black Sea trade route. Recognizing the immense value of controlling this vital gateway, One of her aggressive objectives was to target the weakening Ottoman Empire, Catherine set her sights on expanding Russian territories surrounding the Black Sea to gain access to its lucrative trade opportunities. Russia engaged in two wars against the Ottoman Empire (1768, 1787) and one war against Sweden (1788). These military campaigns allowed Russia to acquire strategic territories and gain control over important trade routes, further enhancing its economic power. With Russia now firmly established along the Black Sea, Catherine facilitated an unprecedented surge in maritime commerce and international trade. The Black Sea region became a bustling hub, connecting Russia to the Mediterranean Sea and beyond. Russian merchants flourished as they exploited the newfound trade opportunities, and the nation's economic growth soared.The Black Sea trade route, once merely a potential gateway, became the conduit through which Russia's economic power and influence surged, leaving a lasting legacy of economic growth and development that endured beyond her reign.

Economic Policies' Conclusion and Comparison

Queen Elizabeth I and Catherine the Great pursued different approaches and achieved distinct outcomes.Elizabeth's reign saw the implementation of a more liberal form of mercantilism, encouraging private investors to collaborate in high-risk ventures and leading to the establishment of massive British joint-stock companies. English colonies, largely developed by individuals, flourished as English merchants and individuals had a genuine stake in their success. Elizabeth's visionary and open-minded approach set the stage for the early development of capitalism in England.Conversely, Catherine the Great adopted a flexible foreign policy, aiming to expand Russian territory, secure strategic sea ports, and promote domestic trade. The focus on aggressive territorial expansion is evident in her military campaigns against the Ottoman Empire. However, the given text lacks specific details on the economic impact of Catherine's policies. In terms of the overall economy, Elizabeth's policies had a profound impact on England's growth and the establishment of early capitalism. Unfortunately, the text does not provide sufficient information to make a comprehensive comparison of the two rulers' economic achievements. It is essential to recognize that the lack of specific data on Catherine's policies hinders a thorough assessment of her economic contributions. If Elizabeth were in Catherine's situation, it is reasonable to assume that she would likely adopt a more aggressive approach to territorial expansion while also maintaining her keen focus on economic growth and stability. Elizabeth's pragmatism and forward-thinking nature might lead her to explore opportunities for trade and territorial expansion, similar to Catherine, while also preserving her emphasis on encouraging individual enterprise and investments for economic prosperity. Her adaptability and

versatility as a leader would likely enable her to navigate the challenges and opportunities of Catherine's circumstances effectively.

Foreign Policy

Compared to England prior to Elizabeth's rule, many other Europeans were far rich and powerful. Spain and Portugal, the most powerful European countries in the 16th century, already established their enormous overseas colonies; each occupying more than 10 million square kilometers. During 1519 to 1521, Hernan Cortes successfully led the Spanish conquest of Mexico. Led to massive silver mining in Mexico and the generation of huge profits for Spain. The conquest made Spain the most prominent player in the silver trade. The Spanish empire was the foremost European power with domination in the ocean by its undefeatable naval power. Whereas England had almost no influence to oversee. England was still a starter during the reigns of Henry VIII, Edward VI, and Mary with very little intention to stretch its influence overboard. The only foundation England had was Henry VIII's naval reforms[22] which modernized the Royal Navy, believing that this could make England recognized as a "worthwhile ally to the Hapsburg Empire."[23] Richard Hakluyt, a 16th-century geographer interested in explorers and travel narratives, suggested to Queen Elizabeth that New World colonies could serve two purposes. First, they could challenge Spanish domination of the New World. Second, the ever-growing poorer classes could be transported there, easing England's population pressures[24].

Prior to Catherine the Great's rule, Russia was relatively behind in terms of territorial expansion and overseas influence compared to the dominant European powers. During the 16th century, Spain and Portugal had already established vast overseas colonies, expanding their territories by over 10 million square kilometers each (source). The Spanish conquest of Mexico from 1519 to 1521, led by Hernan Cortes, resulted in massive silver mining and substantial profits for Spain, making it the leading player in the silver trade. Spain's dominance extended to the seas with an undefeatable naval power. In contrast, Russia had limited overseas influence and territories before Catherine's reign. The Russian empire's territorial expansion was mostly focused on its neighboring regions, with little engagement in overseas colonies. During the early 18th century, Russia's ruling style was turbulent with several weak successors after Peter the Great's death, leading to administrative and economic disorder, as well as internal unrest.

Catherine the Great's foreign policy aimed to change this situation and elevate Russia's status on the global stage. She sought to expand Russian territories through strategic military campaigns and seize key ports from other countries. Her ambition was to make Russia a major player in international affairs and strengthen its influence both economically and politically. Catherine's policies focused on modernizing Russia's administration, military, and economy, in line with her belief in the importance of enlightenment ideas to support reforms in various

[22] https://tudorstuartperspectives.wordpress.com/2015/12/07/elizabeths-age-of-exploration/
[23] Arthur Nelson, The Tudor Navy: The Ships, Men and Organisation 1485-1603, London: Conway Maritime Press, 2001, 42.
[24] https://www.ushistory.org/us/2b.asp

sectors. While England had made naval reforms under Henry VIII to establish itself as a valuable ally to the Hapsburg Empire, Catherine's approach was more assertive and expansionist, targeting strategic territories to bolster Russia's position in the global arena. Her reign saw Russia's transformation into a powerful and influential European nation, as she actively pursued territorial expansion and modernization efforts.

Foreign Policies' Conclusion and Comparison

Elizabeth I's foreign policy was an extension of her domestic approach. She pursued a defensive foreign policy, avoiding conflicts, forming enemies, or engaging in marriage alliances with other countries. At the same time, she encouraged exploration and promoted economic growth through domestic policies, establishing a sense of national identity in England and advancing the institutional system. Her goal was to protect England from the impact of external conflicts while strengthening prosperity and stability internally. Through this diplomatic strategy, Elizabeth I aimed to make England a more advanced nation.

In contrast, Catherine the Great pursued a foreign policy that shifted domestic tensions. She focused on developing Russia by using external wars and territorial expansion to divert internal discontent and conflicts. Catherine employed military campaigns, such as wars against Turkey and Sweden, and the partition of Poland, to expand Russia's territory and influence. This diplomatic strategy allowed her to address domestic issues, divert people's attention, and consolidate her power position.

Overall, Elizabeth I achieved foreign policy success by continuing her domestic policies and enhancing internal stability and economic prosperity. On the other hand, Catherine the Great utilized foreign policy to shift domestic tensions, achieving territorial expansion and increasing Russia's power. Both female rulers adopted different diplomatic strategies, each bringing significant impact and achievements to their respective countries.

According to a working paper by political scientists Oeindrila Dube, of the University of Chicago, and S. P. Harish, of McGill University. They studied how often European rulers went to war between 1480 and 1913. Over 193 reigns, they found that states ruled by queens were 27% more likely to wage war than those ruled by kings.[25] "Moreover, the tendency of queens to engage as aggressors varied by marital status. Among unmarried monarchs, queens were more likely to be attacked than kings. Among married monarchs, queens were more likely to participate as attackers than kings, and more likely to fight alongside allies. The gender norms enabled queens to pursue more aggressive war policies."

One interesting aspect to consider when comparing the two is that they ruled in very different cultures, where the expectations for leaders were drastically different. Therefore, comparing them without considering the context might be arbitrary. Russia once conducted a public opinion survey to select the greatest leaders in its history. The survey results showed that Peter the Great, Catherine II, Stalin, and Putin received relatively high votes, ranking at the top of the list. On the other hand, leaders like Lenin and Gorbachev received significantly fewer

[25] https://www.nber.org/system/files/working_papers/w23337/w23337.pdf

votes and ranked lower. This reflects a certain historical thinking logic among the Russian people.

The leaders who ranked higher in the survey were known for their contributions to expanding the country's territory. Peter the Great and Catherine II were renowned for their territorial expansion and modernization efforts. Stalin led the Soviet Union to victory in World War II and expanded its influence over Eastern Europe. Putin's leadership has been associated with strengthening Russia's geopolitical position and influence on the world stage. In contrast, the leaders who received lower votes in the survey were associated with territorial losses. Lenin presided over the Russian Revolution, which led to the dissolution of the Russian Empire and the formation of the Soviet Union. Gorbachev's policies of perestroika and glasnost contributed to the eventual breakup of the Soviet Union and the loss of its satellite states in Eastern Europe.

Thus, the survey revealed a cultural logic that the only way to legitimize power and be considered as a successful Russian leader, one has to be aggressive in their ruling style, and claiming territory is the best way to show this aggressiveness. Colonization which aims that economic might seems too “soft” for Russians. Thus, in a way, Catherine doesn't have a choice but to possess an expansionist policy. If Elizabeth was in Catherine’s situation, perhaps she would also seek an aggressive foreign policy to secure her legitimacy.

Culture Impact

A Great Monarch should have influence beyond political and economic aspects, culture is a huge aspect in evaluating a monarch’s influence and vision. Elizabeth and Catherine both enriched their nation’s culture; Elizabeth era was known as the renaissance era of England and on the other hand, Catherine’s rule was famous for her westernization of Russia by the enlightenment ideas.

A nation’s Cultural development can reveal a lot about its situation in other aspects. The English Renaissance movements were at its height started by the Elizabethan era and continued throughout the second half of the 16 th century of the reigns of the Stuarts[26]. Under the promotion of Queen Elizabeth, English literacy skyrocketed with increased usage of printing presses. During her reign, some playwrights were able to make a comfortable living by receiving royal patronage. Through famous writers like William Shakespeare, Thomas Wyatt, Spenser, Marlowe, and many others. English culture was enriched, and the English language gained huge international recognition. By the impact of renaissance, England used this chance to spread its culture throughout the world by explorations and colonizations. The center of this culture explosion was the city of London that thrived under Elizabeth’s rule. At this point, London was already the largest city in Europe with a boosting population and flourishing trade. With better living conditions and Queen Elizabeth’s support, public theaters thrived and enriched people's lives. It’s well known that Elizabeth has deep personal interests in theaters. In 1583, she formed her own theater company, the Queen’s Men, of whom her favorite performer was the comic actor

[26]https://www.poetryfoundation.org/collections/154826/an-introduction-to-the-english-renaissance

Richard Tarleton[27]. By the late 1590s, it seems that the Lord Chamberlain's Men had become something of orite with Elizabeth and her court. She favored William Shakespeare and his play as she invited Shakespeare on numerous occasions to perform for her at court.

As a monarch that promoted the Renaissance, Elizabeth's impact even spread to poetry during this time. In The famous Shakespeare play, Macbeth, Lady Macbeth was becoming "unsexed" as she took the dominant role of her husband and her usurper plan. Elizabeth's influence is even more obvious in the Twelfth Night as women in the story dress as males to influence events around them. Those gender bending characteristics in those stories, and the inclusion of compelling female lead characters shows Elizabeth's influence on her subjects[28]. Showing that Elizabeth not only started the English renaissance, moreover, Elizabeth herself is the renaissance. Her ideas and governance is where English people found their renaissance.

The Enlightenment ideas that dominated in Europe especially in France during the 17th soon saw its influence on Russia. Years when Catherine was hoping for a child from Peter, She enjoyed novels, plays, and verse but was particularly interested in the writings of the French Enlightenment, such as Diderot, Voltaire, and Montesquieu[29]. She was extremely well educated, and was hugely influenced by the enlightenment ideas. In her reign, she was known as the sponsor of Russian intellectual aspects such as literature and art. Starting from 1764, Catherine began to buy art from around Europe, and resulted in one the world's most important art collections— the State Hermitage Museum in St. Petersburg[30] that contains more than 4,000 paintings. Prior to Catherine's reign, only about twenty books were published every year, and the subjects were strictly limited to church and religious. After Catherine claimed her throne, she not only hugely supported her subjects to seek intellectual improvement, she also supported the translation of classic books. As a result, many translated works of the Greek, Roman classics and the Enlightenment thinkers arrived in Russia for the first time. This led to the rise of new generation Russian literatures,[31] Besides Catherine's promotion on literature, she also used the theater as a method to promote Enlightenment philosophy, Russian cultural pride, and her power on authoritarian rule.

Although Catherine deeply believed those doctrines, her words are not fully supported by her deeds. Catherine used the Secret Chancellery to investigate and arrest those who are allegedly trying to incite rebellion, and those who were proven guilty of this wrongdoing were punished severely. towards the later years of her reign, Catherine the Great grew more conservative and took actions to reinforce serfdom in Russia. Despite her early interest in Enlightenment ideas and her promotion of intellectual and cultural development, Catherine's focus on maintaining absolute power and the stability of the aristocracy led to a shift in her policies.

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[27] https://www.biography.com/news/did-william-shakespeare-queen-elizabeth-i-meet
[28] https://teachers.yale.edu/curriculum/viewer/initiative_08.01.07_u
[29] Inna Gorbatov, "Voltaire and Russia in the Age of the Enlightenment," Orbis Litterarum 62, no. 5 (2007) [database on-line]; available from EBSCO, accession number 26771756, p. 385 of 393.
[30]https://www.townandcountrymag.com/leisure/arts-and-culture/a38302158/hermitage-museum-catherine-the-great-art-collection/
[31] Vincent Cronin, Catherine, 223.

In 1785, Catherine issued a decree that restricted the movement of serfs, making it more difficult for them to escape the estates of their landowners. This decree effectively tied the serfs to the land, further strengthening the institution of serfdom and limiting their personal freedoms.

Additionally, Catherine increased the power of the nobility over their serfs, allowing the landowners to exercise even more control and authority over their laborers. In 1775, Catherine implemented significant reforms in local administration. The country was divided into 50 provinces, with each province having a population of around 300,000 people. Below the provinces were counties, with each county having a population of approximately 30,000. Governors and county heads were both subordinate to governors-general, who were directly under the central authority, strengthening centralized power. Additionally, the nobility not only possessed all the powers of the old landlords but also had jurisdiction over the entire population within their regions, participating in local administration. This led to the formation of a noble group within provinces and counties to supervise the serfs and prevent uprisings. Furthermore, the feudal government strengthened its supervision and restrictions on the Cossacks in remote areas. In summary, the reforms between 1775 and 1785 further consolidated the rule of the nobility and their monopoly on power within the country.

These moves was in stark contrast to the early years of her reign, where she had considered various reforms to improve the condition of serfs and promote some degree of emancipation.

Conclusion and Comparison

Both Rulers showed a wide and progressive mindset which led major cultural revolutions in their nation. Catherine's reputation as an "enlightened despot" is not wholly supported by her deeds. Catherine the Great ordered absolute obedience from peasants towards landowners and even gifted a large number of her lands and the peasants living on them to the nobility. In total, more than 800,000 peasants were given as gifts to the nobility. This demonstrates that in the 18th century, while England had already begun capitalist production and implemented a parliamentary system, and France had made considerable progress in capitalism, the feudal serfdom system was still prevalent in Russia. While Queen Elizabeth had an enormous impact after her reign not only nationally but also globally. 1606 James I approved the formation of the Virginia Company (named after Elizabeth, the "Virgin Queen")[32].

Final Conclusion

The comparative analysis of Catherine the Great and Elizabeth I reveals two remarkable female rulers who left indelible marks on their respective nations and history. Despite their differences in cultural context and ruling styles, both monarchs displayed exceptional leadership and achievements during their reigns.

Elizabeth I of England was a visionary leader who skillfully navigated through a tumultuous era marked by religious strife and international conflicts. Her defensive foreign policy and pragmatic domestic approach allowed England to prosper and become a major player

[32] https://courses.lumenlearning.com/ushistory1americanyawp/chapter/english-colonization/

on the world stage. Elizabeth's support for the arts and culture, along with her encouragement of exploration, contributed to the flourishing of the English Renaissance and left a lasting impact on literature, theater, and the national identity of England.

On the other hand, Catherine the Great of Russia was a powerful and ambitious ruler who sought to modernize and expand her empire. Her aggressive foreign policy and territorial expansion significantly increased Russia's influence in Europe and solidified her position as a formidable leader. Catherine's patronage of the arts and promotion of intellectual growth brought about an era of enlightenment in Russia and fostered cultural development.

However, both rulers faced challenges and had their shortcomings. Elizabeth's lack of a direct heir led to a succession crisis, while Catherine's early reforms and enlightenment ideals were tempered by later conservative actions and the reinforcement of serfdom. Overall, Elizabeth I's emphasis on addressing domestic issues, fostering national identity, and promoting long-term stability allowed England to flourish and lay the groundwork for future growth. Catherine the Great's aggressive foreign policy and territorial expansion brought short-term gains, but her failure to fully address internal tensions and social issues left underlying problems for Russia to grapple with in the future.

In the end, both Catherine and Elizabeth achieved remarkable success and contributed significantly to the history and development of their respective nations. Their legacies as influential female rulers continue to be a source of inspiration and study, offering valuable insights into the complexities of leadership and the impact of women in positions of power.

How Does the Media Influence Our Political Beliefs? By Binghui Sun

Abstract

The influence of media on our political beliefs has been a hotly debated topic for many years due to the increasing power of the media in our daily lives and the various ways it shapes our thinking. We accept that the media powerfully influences how we view politics and politicians and cast our votes during elections. Consequently, this piece aims to focus more on whether the outcomes of elections genuinely reflect people's will, how psychological theories are applicable in defining how the media can alter our perceptions and beliefs regarding political issues, and the media's role in influencing public opinion, its potential impact on election results, and the dangers of media manipulation. Understanding the influence of the media on our political views is critical and this article will delve into whether change is needed to foster a more authentic voting ideology. This topic is important to me because as a 18-year-old global citizen, I want to have the ability to think critically and I hope I could explore more about this social phenomenon of media influences.

Key Words: media influence, political beliefs, television and radio influence, media narratives influence, celebrities influence

Introduction

The influence of media on our political beliefs has been a hotly debated topic for many years due to the increasing power of the media in our daily lives and the various ways it shapes our thinking. We accept that media powerfully influences how we view politics and politicians and cast our votes during elections. Consequently, this piece aims to focus more on whether the outcomes of elections genuinely reflect people's will, how psychological theories are applicable in defining how the media can alter our perceptions and beliefs regarding political issues, and the media's role in influencing public opinion, its potential impact on election results, and the dangers of media manipulation. Understanding the influence of media on our political views is critical and this article will delve into whether change is needed to foster a more authentic voting ideology.

Television and Radio Influence

The media has been a significant source of information and entertainment since the advent of television and radio. These mediums have significantly impacted how people perceive and interact with political beliefs and issues. Television and radio broadcasts have become integral to public education, disseminating information on current events, history, and politics (İnce et al., 2018, p.10). They have ensured that people understand political decisions better.

The media's substantial influence on politics is evidenced by enabling people to become more actively involved in the political process and providing an arena for political debates and

discourse. Moreover, it has allowed for greater political participation, with people able to access opinions and perspectives on various political issues. As such, they have enabled people to become more knowledgeable and informed on political issues.

Over the years, television and radio have allowed people to engage in political discourse and dialogue (İnce et al.,2018, p.8). This has led to greater political engagement, as people can participate in debates, discuss their views, and even challenge the perspectives of others. People also become more aware of the complexities of politics and diverse perspectives and opinions. Importantly, the advent of television and radio has led to a democratization of information, thus facilitating a broader understanding of political ideologies, and enhancing voter engagement and participation. As such, television and radio have become invaluable sources of information and entertainment and are crucial to the political process.

Media Narratives Influence

Another significant way media influences our political beliefs is through narratives. News outlets often use discriminatory language and frame stories to favor a particular political view (Enders et al.,2021, p.22). For example, a story about a politician's policy may change to make it appear suitable, even if it is harmful. This kind of biased reporting can lead to people believing that a particular procedure is a good idea, even if it is not. Social media narratives have become increasingly influential in shaping people's political beliefs. Users expose themselves to various opinions and statements by sharing content. As these narratives spread, they can shape how people perceive specific issues and, in turn, how they think about politics. In the long run, these skewed narratives can polarize public opinion, lead to misinformation, and potentially influence election outcomes, thus impacting economic, social, and political landscapes.

Social Media Platforms Influence

Politicians use social media platforms such as Twitter, Facebook, YouTube, and Instagram to spread political opinions and news (Shafaq et al.,2022, p.12). They post blogs and website links allowing citizens to access relevant information. The citizens also interact and raise their concerns by replying to their leaders. Political videos are often uploaded to platforms like YouTube, where citizens can stay updated on critical political debates, news, and political progress of their time. However, these platforms are not immune to misinformation. For example, the "Pizzagate" conspiracy theory that circulated during the 2016 United States presidential election illustrates how false information can manipulate public opinion.

Celebrities and Influencers

Celebrities and influencers often have a large following on social media, which gives them the power to promote particular political views and candidates. They can also use their influence to sway public opinion, significantly impacting voting behavior. This power is often harnessed due to the trust and admiration people place in these figures, leading to a willingness to adopt their political leanings without critical evaluation. This inevitably shapes public opinion

and mobilizes people to act on important issues. They can sway the masses' opinion and influence public policy decisions (Kiran, 2020, p.710). For example, in 2020, celebrities like Taylor Swift, Oprah Winfrey, and former First Lady Michelle Obama endorsed presidential candidates and encouraged their fans to get out and vote. Influencers often use their platforms to share their views on current events, create conversations around controversial topics, and call for action. Shaping public opinion and compelling people to support specific causes or candidates can significantly impact voting behavior.

Conclusion

In conclusion, various forms of media have a powerful influence on our political beliefs. These media platforms shape our attitudes, opinions, and beliefs about the political world by providing various information sources. Through carefully crafted messages, these sources can shape how we view current issues, candidates, and policies. Influencers, celebrities, and other public figures can reinforce our beliefs by being an example. Therefore, while these platforms have the capability of reaching a wider audience, encouraging meaningful discussion and debate, and providing a platform to express our views, it is crucial to approach this information with critical thinking and discernment, thus ensuring the creation of well-informed and authentic voting ideologies.

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Impact of Limited Maternal Healthcare in Developing Regions By Aanya Munagala

Abstract

This paper examines the role of maternal healthcare in developing countries around the world. The maternal mortality rate in rural areas is significantly higher than the mortality rate in developed countries. Newborns and mothers are at high risk for mental health issues, physical health complications, and death in these countries.

Incorporating evidence from reviews, scholarly studies, and renowned public health sites, this study demonstrates the specific factors that create discrepancies in maternal healthcare along with possible solutions. It argues for increased community engagement programs and a focus on maternal mental health. Additionally, this study touches on the cultural importance of specific traditions and how to integrate modern medicine into these societies.

Introduction

Millions of women around the world face the constant threat of maternal mortality despite living in a progressing world. In developing areas, the need for healthcare has created a crisis; women are rarely given the necessary treatment to healthily maintain a pregnancy, and this can often result in high maternal mortality rates. Healthcare for women is a complex subject. Women face unique issues of menstruation, pregnancy, cervical cancer, and menopause. These conditions highlight the need for specific and targeted care, but in most of the world, this is lacking. Maternal health is defined as the health of women during their pregnancy, childbirth and postpartum period. During pregnancy, women need regular access to doctors, totalling to about 15 checkups (U.S. Dept. Health & Human Services). While pregnant, the health of the mother is particularly precarious. Their diet must be regularly monitored to ensure healthy consumption of folate, iron, calcium, and protein. A mother's weight must also be monitored in order to confirm it is not exceeding a healthy threshold. Depending on the person, other prenatal vitamins may also be necessary (NIDDK). Ultimately, women in developing areas may not be able to maintain a nutritious diet with daily breakfasts and moderate exercise. Due to the lack of resources, pregnant women in these places are at a significant disadvantage for their health and will likely face birth-related complications. After giving birth, women need an increase in their food consumption– at least a five hundred calorie increase. Without dietary needs being met, or other regular care, new mothers are at high risk for bleeding, sepsis, and hypertensive disorder (UNFPA). Addressing global maternal health inequities requires targeted healthcare infrastructure and community engagement to combat the mortality rate and mental health issues that come with being a mother in certain regions.

Maternal Mortality in Developing Countries

Women's health has historically been an underfunded and under researched field. For women in developing areas like Africa and South Asia, receiving care is a complicated and unlikely task. This is incredibly harmful and can lead to high maternal mortality rates. In 2020,

the global maternal mortality rate was 223 deaths per 100,000 live birth births. However, in least developed countries, this number can go up to 377 (UNICEF). This statistic can be amplified by the fact that 99% of all maternal deaths occur in developing countries (WHO). There are a myriad of reasons as to why women in certain regions are at higher risk for death during the maternal period, but it can be general consolidated to a few things. Mothers who lack sufficient prenatal care and care during delivery have a higher chance of death (WHO). In rural areas, education can also play an important role in mortality rates. Women and families who have limited education can make uninformed decisions about family planning. Dangerous timings between births is also a risk factor; in order to ensure this is avoided, couples and women especially must space out pregnancies appropriately. The Mayo Clinic suggests waiting at least 18-24 months between pregnancies, but in developing countries, approximately one-quarter of pregnancies occur within the first 24 months (Molitoris). In these scenarios, the baby is at higher risk for problems like low birth weight, congenital disorders, and premature birth. However, the mothers are at increased risk for maternal anemia and other health related issues (Mayo Clinic). Certain cultural practices can also have an impact on maternal mortality; in many rural areas, girls who are of low status will experience neglect. Girls who are pushed into early marriages will likely have children at a young age, which can create more dangers (NIH). Developing countries generally have higher rates of domestic abuse which can be detrimental during pregnancies. If a woman were to exert herself too much, she would be at high risk for hemorrhaging. Domestic abuse in a physical sense proposes threats to a mother's body and can have effects on her health (Christaki).

The life of a mother is not only important because of her own bodily autonomy, but because of her role in the family. Economically, women dying in childbirth or during the pre/post-natal period can cause significant financial hardships for the families they leave behind. The loss of a parent is also equivalent to the loss of an income, and in developing areas, most families cannot afford to lose an income source. In a study focusing on families in Ethiopia, it was concluded that children whose mothers died around the time of childbirth had fifty times greater risk of dying within the first month of life (Moucheraud). The health of babies is directly impacted by the death of a mother. Without fresh breast milk, babies in certain areas are often fed contaminated water or chemical substitutes for breast milk which can stunt their growth. Family structures are often ingrained into cultures in South Asia and Africa, and although they can provide strong relationships, they can also be harmful when mothers pass away; children may have to be moved to other families which can create tensions and lead to child marriages, young labor, and lower chances of receiving a comprehensive education.

Access to Prenatal and Antenatal Services

If a woman were to get pregnant in a place like Africa, it would be difficult to find a doctor they could regularly visit. One of the largest issues with women's health in places like Africa or South Asia is the very limited health care facilities. Aside from the scarcity of developed hospitals, transportation can also be difficult. Limited infrastructure to take women to

the hospital can turn traveling into a costly and timely affair (Dahab). Many times the facilities that do exist carry limited supplies and the drugs they do have cataloged are out of stock. These obstacles can be discouraging and can lead to expecting mothers to avoid getting the help they need (Islam). There are also severely low numbers of trained professionals assisting with births in developing countries. In fact, in only 20% of births are trained professionals attending to the mother during births (WHO). Some programs have been created to help combat some of the barriers restricting women, such as Maternity Waiting Homes and the Maternal and Child Health Integrated Program funded by United States agencies. This program works with developing countries all over the world. The goal of the Maternal and Child Health Integrated Program is to target the prevention of postpartum hemorrhages, pre-eclampsia/eclampsia, and help expand access to skilled birth attendants. The program's methods to lead this change include focusing on competency-based training with "supportive supervision" while also making training courses increasingly abundant. This program is effective because it directly targets one of the leading causes of high maternal mortality rates, but also ensures better health for the mother and child by addressing concerns regarding nutrition, malaria, HIV, and family planning (MCHIP). Another program that has successfully supported expecting mothers is the system of Maternity Waiting Homes. Maternity Waiting Homes implement waiting homes near hospitals and clinics for women to use as they approach their due dates. The effectiveness of these waiting homes was questioned in a study that eventually concluded the women who used the waiting homes were 80% less likely to die than nonusers. Waiting homes can also help reduce more than two thirds of stillbirths. Ultimately, women in South Asia and Africa are victims of high maternal mortality rates due to the lack of resources to help combat limited healthcare access, birthing professionals, and nutrition. However, it is possible for programs and agencies to combat these issues by using targeted methods to help increase the access women have to effective care.

Child Marriage and Adolescent Pregnancy

Child marriages and adolescent pregnancy are also connected to high maternal mortality rates in developing countries. Child marriage is defined by any marriage in which at least one party is under the age of eighteen. It is also implied that child marriages can be considered forced marriages because at least one person cannot fully consent to the union. In the least developed areas, about forty percent of girls are married before their eighteenth birthday. Additionally, twelve percent of girls are married before they turn fifteen in these areas (OHCR). Child marriages can lead to numerous issues among young women; some are social, but others are physical. Some girls may flee their homes or commit suicide to avoid these marriages. Child marriages typically come with early and frequent pregnancies which results in high maternal mortality rates. Young mothers are less likely to receive necessary care to maintain a pregnancy, and there are also complications with younger bodies. Young women do not have matured enough bodies to ensure a healthy pregnancy. Globally, over 22,0000 girls die from pregnancies resulting from child marriages. Women who become pregnant during their twenties are significantly less likely to die because their bodies have developed enough to carry a child to

term (Save the Children). According to a 2019 study, 55% of pregnancies among girls ages 15-19 result in abortions which are often unsafe (WHO). These pregnancies from child marriages can take an emotional and physical toll on the young girl carrying the child. Unsafe abortions have high mortality rates and can often result in death. There are additional risks for early pregnancies, such as increased chances of eclampsia, puerperal endometritis, and systemic infections. Girls under the age of eighteen are at much higher risk for these compared to women ages 20-24. Eclampsia is a condition that causes convulsions in pregnant women as a result of high blood pressure. Convulsions can be followed by a coma status which can be dangerous for the mother and child. Puerperal Endometritis is an infection of the pregnancy endometrium which can have an effect on all layers of the uterus. These combined risks can be detrimental to young pregnant women, and highlight the dangers of child marriages. Child marriages are often arranged out of the need for money. In developing areas, it can seem unlikely for a daughter to find a job and provide for her family. Instead, marriage may be the more financially efficient option. However, providing an education to girls can help stop child marriages and solve the financial crisis. Education will allow girls to enter the workforce and find a decent job without marrying young. Additionally, child marriage is a cycle; families that have young mothers who married young are more likely to continue that pattern in future generations. In order to break this cycle, women must be provided an education which will allow them to have child marriages and early pregnancy. Aside from distancing themselves from these practices, it will allow for their children to also have a lesser chance of entering a child marriage (UNICEF).

Cultural Practices

In places like South Asia and Africa, cultural practices severely affect maternal health. In many places in Africa, female genital mutilation is incredibly common. Female genital mutilation is defined by the WHO as all procedures the involve “partial or total removal of the external female genitalia, or other injury to the female genital organs.” Female genital mutilation is never necessary and is often detrimental to the anatomical health of the woman. FGM is common in Africa, the Middle East and Asia in about thirty countries. FGM can cause severe bleedings, complications with urinating, cysts, and infections. However, FGM can be even worse during childbirth (WHO). Female genital mutilation is viewed as a way to monitor and control a woman’s sexuality–especially before marriage. Adolescent girls between infancy and the age of fifteen are at the highest risk of FGM. FGM can ensure virginity before a marital union and can also ensure fidelity afterward. However, there are more than controlling motivations encouraging FGM in rural areas. In fact, FGM is rooted into many cultures. In order to fully remove FGM as a threat, mindsets of those in power need to be altered in order to rid communities of sexist beliefs. FGM is almost always detrimental to the health of the women and causes high likelihoods for complications in pregnancies. Female genital mutilation can lead to complications such as difficult deliveries, excessive bleeding, Cesarean sections, and in some cases resuscitation of the baby may be necessary. Today, 200 million girls and women have been experienced female genital mutilation at some point in their life. Culture can play an important

role in maternal health in other ways as well. Some women may not trust western medicine as much and instead may prefer birth attendants who practice traditional medicine. Traditional medicine in these areas typically follow holistic approaches and focus on herbs and spirituality. Western medicine can seem as though it's infiltrating the lives of community members, and this is one of the flaws of western practices. However, the lack of access to maternity healthcare is also a barrier that increases the use of traditional medicine. If modern medicine is unavailable in most rural areas, it will discourage women from seeking it out and they will most likely revert to the cultural practices they have been historically relying on for centuries. Traditional medicine is information that has been passed down for generations and has more of an intimate connection than western medicine. It is also possible for attending physicians to have dismissive attitudes about cultural and traditional practices (Shewamene). In order to truly improve maternal health in developing areas, it is vital to approach the situation with cultural sensitivity. Traditional medicine may be what is best for some of the women in these communities, but it's evident that there is a severe lack of trained medical professionals available to assist women and this can be discouraging. By making professionals more common, women can make informed decisions and choose what type of healthcare they would like, but it's the ability to make this decision that is important.

Healthcare Infrastructure

Maternal health is largely impacted by infrastructure, especially in developing areas. Most hospitals do not have the necessary funds to properly manage a maternity ward. There are uneven funds and human resources along with severely limited institutional capacity and infrastructure. Within hospitals, there are also weak information systems (APHA). In developing areas with few resources, it can be particularly hard to properly distribute funds to support a maternity sector of a hospital or clinic. The WHO estimates that about four million more doctors and medical workers are necessary to achieve 80% of essential care which highlights the growing need for this improvement. The best way to do this is to open more hospitals focused on maternal health in order to guarantee mothers are being properly taken care of. Transportation to modern medicine sites can also prove to be troublesome; worn out and unpaved roads can be difficult for pregnant women and can be discouraging. In certain areas, there may be adequate hospitals but the infrastructure allowing expecting mothers to go to these places may make the journey futile. In order to successfully improve maternal health in these regions, initiatives must be taken to ensure that there are no barriers whatsoever stopping women from going to a hospital–including maintaining roads and building women's sectors of clinics.

Role of Community Engagement

Although these types of initiatives are important and vital to the growth of maternal healthcare globally, community engagement is equally, or if not more important. Community health workers vary from typical medical professionals; a CHW is someone who is a member of a community but is chosen to provide basic health and medical care to those in need. Since 2003,

Ethiopia has begun this movement by training thousands of community health workers to specifically target inequities in maternal health systems (Lassi). The process of appointing and growing community health workers is a healthy and engaging way to combat systemic issues; it will allow for communities to strengthen their relationships and become more of a co-dependent society. Investing in community health will guarantee care for mothers in remote areas. Community health workers can also focus on care from preconception to delivery and studies have shown that interventions during the preconception time period are connected with lower neonatal mortality rates and increased antenatal care. Another way CHWs differ from traditional healthcare workers is that it is easier for them to provide home visits. In Bangladesh, India, and Pakistan, growing numbers of community health workers who could engage in home visits reduced the newborn death rate by 30-61% in some situations (Lassi). Community health workers (CHWs) can also improve breastfeeding practices and increase healthy habits after birth. In a progressing world with growing technology, it is important for medical practitioners to take advantage of mobile health. This is something both hospitals and community health workers can utilize to improve maternal health. Mobile health (mHealth) has been a growing field, and for good reason. Mobile health will allow for timely and efficient data collection but also the training and monitoring of CHWs to ensure their performance is suitable. Despite growing infrastructure and resources in some areas, it is beneficial for primary care services to have direct connection to women, and community health workers can be the key to this (Lassi). The lack of family planning is a factor that can endanger the lives of women by leading to frequent, unhealthy pregnancies. This is another field CHWs can assist in. Another study in Ethiopia proved this by putting young women into a 2.5 year outreach program (Bang). This program consisted mostly of media use and health education for women of reproductive age in the community. Health care providers were also trained during this program and taught how to deliver care to pregnant women. An institutional birth rate is a rate measured by births in established hospitals, and after 2.5 years, it was shown that the institutional birth rate increased from 10.8% to 93.5% (Bang).

Maternal Mental Health

There are more risks to maternal health than physical problems. In fact, maternal mental health is one of the largest issues around the world, but specifically developing areas. Globally 10% of pregnant women and 13% after giving birth have some sort of mental disorder. In most cases it's depression, but it could also be other disorders such as anxiety. In developing areas, the statistics are even more dramatic with 15.6% of women during pregnancy and 19.8% after giving birth experiencing a mental disorder (WHO). Mental health during the pregnancy period is very precarious and women are more likely to develop disorders during this time (Wilson Center). Although depression itself is an issue to combat in these areas, it is especially dangerous because it can lead to suicide. In fact, suicide is one of the leading causes of death in young women. Treating the depression of mothers can be beneficial not only for mothers, but for the children as well; improving the mental state of a mother can lead to improved growth of newborn and lower

chances of malnutrition (Shidhaye). Maternal depression puts infants at higher risk for preterm birth, low weight, and worsened cognitive development. Women in developing areas are at higher risk because poverty, migration, stress, violence, and natural disasters are all risk factors for mental disorders (WHO). Mental health programs are particularly hard to establish in these areas because governments from low- and middle-income countries (LMICs). In fact, they spent the lowest percentages globally on mental health initiatives. Human resources are incredibly limited in these areas, and in LMICs, 75% of people who need help do not receive it (Mascayano). The lack of necessary programs can help contribute to a growing stigma in developing areas. Knowing receiving help is difficult can be discouraging and inflict shame on those struggling with mental health. The WHO is committed to strengthening the information system and growing research in the field of maternal mental health. Although statistics are available, there is still limited general knowledge, so increasing mental health outreach programs is necessary. One of the main goals of the World Health Organization is to support programs with maternal and child health initiatives. Making routine antenatal and postpartum health services could be incredibly beneficial as they may allow diagnoses to happen early in the development of a disorder. It is also important to focus on people at high risk and to understand the people who are more susceptible to developing depression. Ultimately, mental health is a significant part of maternal health, yet it is not viewed as such. In order to fully improve maternal health, there must be a focus on mental health as well.

Conclusion

Maternal health has been a field that has historically been underfunded and under researched. Women in developing areas are at a particular disadvantage with limited healthcare access. From birth, women in places like South Asia and Africa are often treated as second-class citizens. With limited education, many girls are unaware of the importance of maintaining female health and family planning. Adolescent girls are at risk for female genital mutilation which has no health benefits and is incredible detrimental. FGM can cause future complications in childbirth which can lead to death for the mother. There are other risks like child marriage. Child marriage often deprives girls the opportunity to pursue an education because it is perceived as though marriages will provide financial support. However, child marriages are linked to early pregnancies which can be dangerous. Young bodies are not fit to maintain a pregnancy and there will likely be complications, or even death. The maternal mortality rate is a clear signal that healthcare in developing countries is severely lacking, especially because 99% of all maternal deaths occur in these areas (WHO). Maternal mental health is another aspect of women's health that needs additional support and research. In rural areas, stigmas surrounding mental health are prevalent and this is typically due to a lack of resources. It is common for women to experience depression during the pregnancy time period, but women in developing areas are at even higher risk because of poverty, stress, and environmental factors (WHO). Addressing maternal health challenges globally requires targeted healthcare infrastructure and community engagement to combat the mortality rate and mental health issue. Healthcare infrastructure is severely limited,

and in order to improve this, more hospitals/clinics need to be established. Improved transportation is also necessary to ensure traveling is significantly less troublesome than it currently is. Community engagement projects can be another effective way of improving maternal health. CHWs provide for direct channels between primary care providers and community members, while also ensuring women are receiving regular care. An important aspect of any intervention is to be culturally aware; the goal of increasing healthcare access should not be to strip away any cultural integrity, but should instead allow for traditions to prosper while creating more opportunities for growth.

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The Effects Of Conformity On Ethnic Identity By Ananya Uddanti

Introduction

The American Century is marked by the USA's rise to power in the global sphere due to the welcoming of immigrants in the post-WWII era (Hirschman 595). Immigration — the leading cause of population growth in the USA — has added to the diversity of the social and cultural landscape of the USA (Hirschman 603). As the USA arose as the hub of novel ventures, success, and support, likewise creating an image of the uttermost happiness, economic success, beautiful entertainment, fashion industry, and cutting-edge technology, the USA led young immigrants to believe that the USA was a place to fulfill their dreams of success (Webb 41). However, the idea of success manifests itself in adolescents of cultural backgrounds, leading them to believe they must modify themselves to meet success. In the 2003 novel *The Namesake*, Gogol wants to succeed and believes that his name, representing his cultural and familial identity, stands in the way of his success. However, his obstacle is not external but rather an internal self-conflict. Gogol's wish to shorten and modify his name is a fictitious example of an immigrant child wanting to conform to the norms around him to 'fit in' and consequently disregarding the cultural significance of his norms. This idea of conformity can be of great importance in one's adolescence. During development, adolescence creates a desire to establish an identity and find a place within existing social groups (Do et al.). Adolescent immigrants were denied the traditional upbringing of their native country while simultaneously denied absorption of the USA's culture (Ueda). This creates feelings of discomfort, as can be seen in Gogol, describing that he had "been lazy, addressing his parents in English, though they continue to speak to him in Bengali… he wanders through the house with his running sneakers on… [during] dinner, he sometimes uses a fork" (Lahiri 89). Describing aspects of Bengali culture (i.e. eating with hands), Gogol notes his conscious rejection of these traditions, engaging in American ways of life, and feels regretful in his actions.

There are a few key terms that must be defined. Culture is a pattern of values, while assimilation is the process of socialization into the values and customs of the host country (O'Flannery 195). Race refers to genetically and biologically distinct groups, while racial identity relates healthy psychological activity to the social and political implications of one's race; ethnicity, however, refers to similar characteristics but extends to historically distinct cultural groups (Holcomb-McCoy). For this paper's scope, both ethnic and cultural identities will be treated synonymously due to their interdependence. This paper aims to evaluate how cultural conformity and ethnicity in adolescence affect the formation of one's identity in the American Century.

Exploring the Relationship

Early adolescence is a crucial period marked by changes to life structure, as this is when children begin to ponder their identity and their place in the larger scheme of the world, all while maturing (Holcomb-McCoy). Citing Erikson (1968) and Ponterrotto and Pederson (1993),

Holcomb-Macoy notes that the inability to gain an identity during this period leads to the presence of adverse feelings, such as confusion and despair, due to the extensive process of commitment necessary to form an identity. Therefore, forming a healthy ethnic identity is crucial to future healthy self-view and healthy multicultural scenarios. The development of identity requires the development of an individual's and group identity, where group identity is essential among members of minorities. In contrast, individual identity refers to the Western influence, making it essential for assimilation experiences (Phinney).

The formation of both identities is vital and takes place during adolescence. Per Halcomb-Macoy, the first stage consists of early adolescents lacking exposure and interest in ethnic identity and its complex nature. As seen in the description of Gogol's room, "the Lennon obituary pinned to the bulletin board, and then a cassette of classical Indian music… still sealed in its wrapper." (Lahiri 29), Gogol prefers the parts of his life related to Western American ideas, over the Bengali portion of his life. Gogol engages in the pop culture of the American youth, simultaneously with the lack of acknowledgment of Indian culture, indicating his conflict with his name occurring at a period in which his identity has been fully developed. As they grow, the adolescent acknowledges their ethnic culture and differentiates it from their surrounding predominant culture, facilitated by the expansion of knowledge of their culture and profoundly moving emotional experiences. Finally, the adolescent gains a deep appreciation for their ethnicity that evolves into pride, which led Halcomb-Macoy to hypothesize that adolescents in the later stage of life are more aware of their ethnic identity.

Adolescents conform when it benefits them (Do et al.). However, what is deemed a 'benefit' varies the standards of what makes something beneficial change, depending on the situation and one's self-made ideals. Do et al. find that an individual's self-related agenda and goals change their decisions about conformity. By that means, conforming to the culture surrounding them is beneficial when needing to form friends and not wanting to stand out; however, conforming may not be ideal in situations where cultural identity is tarnished. In a study of Puerto Rican immigrants, O'Flannery noted that the group deemed socializing with Americans vital and normal since they lived in integrated societies in America (202). Likewise, in The *Namesake*, there is an incident in which"[Gogol] wishes he could disguise it [his name]… the way the other Indian boy in his school, Jayadev, had got people to call him Jay" (Lahiri 78). In this scenario, Gogal needed to modify his name and conform it to American ideals. Thereby, as is evident in certain scenarios, conforming and adjusting to the American landscape by interacting with Americans is crucial and considered beneficial by adolescents; this is consistent with the notion from Do et al. that adolescents conform based on their social setting.

Furthermore, the interaction with Americans is crucial: O'Flannery states the need for social conformity to be greater than that of cultural conformity, noting the immigrants' social base shrinks upon immigration from their origin country (196). Hence, the immigrant must establish new social relations to achieve a sense of self-identity, understood as what those above the Puerto Rican study group aimed to achieve through their interactions.

However, immigration assists with the dismantling of native social and cultural systems, as immigrants strip themselves of old cultural practices due to these interactions (O'Flannery 202). Hamermesh and Trejo believe that the discomfort immigrants feel in the socialization process that comes with assimilation is why certain groups of immigrants can minimally and cautiously participate in assimilating activities, defined as shopping and socializing. This is consistent with the notion that, in some instances, isolation from natives can benefit an immigrant's academic performance in terms of better performance in a school predominantly of their ethnic group (Bottia). Concerning the aforementioned discomfort noted by Hamermesh and Trejo, the presence of individuals of the same ethnicity and culture provides an improved atmosphere with a distinct lack of socio-cultural barriers. Nonetheless, when adolescents become aware of racial/ethnic boundaries as they develop an ethnic identity, they distance themselves or may be more conscious of the boundaries around them (Halcomb-Macoy). Once again, as per Do et al., adolescents are very aware of their social setting and can shift their decision on whether or not to conform based on the setting. This shift is consistent with the isolation noted by Halcom-Macoy and the assimilation by O'Flannery. Therefore, the key to healthy identity formation, Phinney believes, is assimilation, in which a new identity containing the aspects of the origin and host cultures are combined and can be formed. However, the contrast in solutions of assimilation by Phinney and isolation by Bottia, Hamermesh, and Trejz indicates the ideal solution and approach to a healthy identity is a median to the aforementioned solutions.

Schools can serve as a vessel for the formation of a healthy identity. Immigrant students are allowed to receive education and socialize traditionally through schools while increasing tolerance and positivity and lowering long-term prejudice (Bottia). Ueda notes public schools of the 'Progressive era' as an entity that allows for social and civic engagement meant to counteract the differing origins of the schoolchildren. Increased education attainment is related to increased participation in assimilating activities (Hamermesh & Trejo). Ueda notes that second-generation immigrants were denied the traditional adolescence of their native country while simultaneously struggling to absorb their host country's culture. This introduces the need for schools to introduce second-generation immigrants to American ideology. Likewise, Ueda finds a need for ethnic schools that teach adolescents their native language. Acquiring a person's native language ensures proper communication and a lack of conflict between parent and child, and such language schools serve as a nexus for ancestral knowledge, respect, and love for the native/ethnic culture. This again introduces the concept of isolation from host culture and its benefits, as mentioned by Bottia. Thereby, schools, which can serve as vessels for conformity and ethnic development, are crucial to a healthy and satisfied individual, in contrast to the view presented by Phinney, in which assimilation is vital.

Educators also play a vital role in the development of the ethnic identity of the student. In a parallel relation between student and educator, both have the same level of development, while a regressive relationship is one in which the educator suppresses ethnic identity development due to educators possessing a less developed ethnic identity (Holcomb-Macoy). Therefore, to develop the ideal ethnic identity such as the one mentioned by Phinney, a progressive

relationship must exist, as the educator possesses a more developed ethnic identity and can thereby assist the student with their development (Holcomb-Macoy).

Forming a healthy ethnic identity is associated with various benefits, all of which make it ever more important to provide adolescents with a healthy development process not hindered by conformity. A study by Halcomb-Macoy found that adolescents with more positive views of their ethnicity are less likely to use unhealthy coping mechanisms and less likely to display aggression. The formation of ethnic identity was related to decreased drug use (Halcomb-Macoy). Moreover, there is a positive correlation between ethnic identity development and self-esteem (Rumbaut). There is also a correlation between ethnic identity and academic achievements (Halcomb-Macoy). Though immigrant parents possess lower levels of education, their immigration to the USA comes with hope and acknowledgment that education is the key to betterment (Bottia). Migration to the USA demonstrated parents' desire for their children to obtain a proper American education, and the economic cost of this desire pushed their children to work harder in school (Ueda).

However, these benefits do not mean that there should be no conformity in one's adolescence. Boen and Hummer find that immigrants are vulnerable to stressors associated with assimilation, such as their status and naturalization process, language barriers, etc. Likewise, Angelini et al. find a direct relationship between the level of cultural assimilation, in terms of linguistic and ethnic differences, and immigrants' emotional well-being, indicating a need for action on behalf of the host nation to catalyze cultural assimilation. These stressors serve as evidence to indicate that immigrants will consistently need to assimilate, to some extent, to achieve a sense of self-satisfaction in the USA. Otherwise, the aforementioned stressors continue throughout an immigrant's life, and the repetitive experience of the stressors can result in chronic responses which can later lead to psychological and physiological damage; the prolonged stressors, stemming from societal barriers, will result in a lower quality of improved living, indicating the need for some sort of assimilation to be healthy in the USA (Boen & Hummer).

Conclusion

This paper aimed to evaluate how cultural conformity in adolescence affects the formation of their ethnic identity in the American Century. A clear argument can be made for the case related to conformity and healthy identity formation: there must be conformity and ethnic/cultural identity development occurring. Though the extent to which each is needed is vague, there is a clear need for both. It must be noted that schools facilitate both processes, and the solution to achieving a harmonious state between conformity and ethnic identity lies in interventions through schools. Conformity assists adolescents in creating a social network and avoiding sociocultural stressors. Likewise, a healthy and fully developed ethnic identity ensures the adolescent performs well academically and actively avoids prejudiced behaviors. Therefore, there is a need for a balance between both conformity and ethnic development in adolescents.

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