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MALAT1 Facilitates Progression of Liver Disease

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Abstract: Liver-related diseases, including nonalcoholic fatty liver disease (NAFLD), acute liver injury (ALI), and hepatocellular carcinoma (HCC), represent a major global health burden with limited effective treatment options. Increasing evidence depicts the long non-coding RNA, MALAT1 as a key regulator of liver disease progression through its disruption of protective cellular pathways. This review examines the molecular mechanisms through which MALAT1 contributes to hepatic dysfunction, with a focus on N^6-methyladenosine (m^6A) RNA modification, interactions with the epigenetic regulator EZH2, and interference with microRNA signaling. M^6A modification, mediated by enzymes such as METTL3 and reader proteins including YTHDC1, enhances MALAT1 stability and expression, amplifying its pro-inflammatory and pro-fibrotic effects. MALAT1 also recruits EZH2 to silence genes essential for mitochondrial homeostasis and hepatocyte regeneration, thereby exacerbating liver injury. In addition, MALAT1 functions as a competing endogenous RNA that sequesters protective microRNAs, particularly miR-206 and miR-22, leading to metabolic imbalance and increased cellular vulnerability. Together, these pathways position MALAT1 as a central driver of liver disease progression and highlight its regulatory network as a promising target for future therapeutic development.

Keywords: MALAT1, m^6A modification, liver disease, EZH2, microRNAs

Introduction

Liver-related diseases, including nonalcoholic fatty liver disease (NAFLD), acute liver injury (ALI), and hepatocellular carcinoma (HCC), result in 1 out of every 25 deaths worldwide, representing a major global health issue (Cleveland Clinic, 2023). However, despite liver-related illnesses becoming more prevalent worldwide, there are currently few effective treatment options. MALAT1 is a long non-coding RNA (lncRNAS) that has been associated with the progression of liver related-diseases. LncRNAs are RNA molecules longer than 200 nucleotides that are essential for controlling transcriptional, post-transcriptional, and epigenetic aspects of gene expression (Chen, Kang, et al., 2022). Additionally, lncRNAs are important modulators of cellular function, influencing processes like splicing, microRNA regulation, and chromatin remodeling (Chen, Kang, et al., 2022; Xiang et al., 2022). By binding to proteins and microRNAs, lncRNAs change signaling pathways and gene transcription, acting as a competing endogenous RNA and molecular scaffold (Chen, Kang, et al., 2022; Shu et al., 2021; Chen et al., 2020; Xiang et al., 2022). One of the most highly conserved and widely expressed lncRNAs among them is MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) (Wang et al., 2018). MALAT1 plays a crucial role in liver disease by interfering with defense mechanisms thereby promoting pathological processes, such as lipid buildup, fibrosis, apoptosis, and impaired regeneration (Shu et al., 2021; Chen, Kang, et al., 2022; Xiang et al., 2022). Despite the established association between MALAT1 and liver diseases, the mechanism by which MALAT1 influences liver disease progression and outcomes are not well understood. This paper will discuss MALAT1 upregulation, through m^6A modifications and interactions with other proteins and RNAs in the context of liver related diseases. Understanding the interactions within these pathways and how MALAT1 is regulated could serve as potential therapeutics for liver related-diseases.

M^6A RNA Modification and MALAT1 Stability

Role of m^6A Modification in Regulating MALAT1 Levels

The most abundant internal RNA modification in eukaryotic cells which plays a vital role in regulating post-transcriptional gene expression is m^6A modification (Chen et al., 2025). The N^6-methyladenosine (m^6A) modification is methylation of adenosine at the N6 position of an RNA molecule (Chen et al., 2025). This modification influences multiple aspects of RNA metabolism, including splicing, translation, localization, and stability (Chen et al., 2025). In liver-related diseases, growing evidence suggests that dysregulated m^6A methylation contributes to disease progression by altering RNA function and expression patterns (Feng et al., 2024). The lncRNA MALAT1 has emerged as a prominent downstream target of this regulatory mechanism (Chen et al., 2025). Literature reviews of liver cancer also highlight that the addition of methyl groups to specific adenine residues on the MALAT1 transcript promotes tumor growth and immune evasion by altering the activity of the lncRNA (Chen et al., 2025). These chemical modifications, carried out by enzymes which add the m^6A modification (writers) such as METTL3 are recognized by proteins (readers) like YTHDC1 that attach to modified RNA. METTL3 and YTHDC1 are thereby able to regulate the function, alter the structure and interactions of MALAT1, enhancing its stability and biological activity. Consequently, m^6A modification functions as an upstream regulatory process that strengthens MALAT1's pathogenic influence in liver diseases, including acute liver injury, fibrosis, and hepatocellular carcinoma (Shu et al., 2021; Chen et al., 2025).

METTL3-Driven m^6A Modification of MALAT1

Recent studies have provided direct evidence that m^6A methylation promotes MALAT1 expression and pathogenic function in liver fibrosis. Shu et al. (2021) demonstrated that in Kupffer cells (KCs), the liver's resident macrophages, m^6A modification of MALAT1 is significantly upregulated during both in vivo liver fibrosis and in vitro M1 macrophage polarization. M1 macrophages are highly detrimental in chronic liver disease because they are the primary pro-inflammatory cellular agents that sustain inflammation. Specifically, the m^6A writer enzyme METTL3 was found to be overexpressed, leading to an increase in MALAT1 methylation levels (Shu et al., 2021). This modification elevated MALAT1 abundance, which in turn facilitated its interaction with PTBP1, promoting USP8 mRNA degradation (Shu et al., 2021). The loss of USP8 disrupts its regulatory control over TAK1 ubiquitination, thereby enhancing macrophage pyroptosis and inflammatory signaling (Shu et al.,

2021). These results established that METTL3-mediated m^{6}A methylation acts as an upstream mechanism that stabilizes MALAT1 and amplifies its pro-inflammatory and pro-fibrotic functions (Shu et al., 2021). Consequently, m^{6}A modification links epigenetic regulation to the persistent activation of macrophages that contributes to liver fibrosis progression through the METTL3–MALAT1 axis (Shu et al., 2021).

Stabilization of MALAT1 via YTHDC1 and PXR During Oxidative Stress

Beyond its role in fibrosis, m^{6}A modification also regulates MALAT1 expression during oxidative stress in liver cells. Feng et al. (2024) found that m^{6}A methylation recruits the reader protein YTHDC1, which binds to MALAT1 and prevents its degradation. This interaction stabilizes MALAT1, allowing it to accumulate in hepatocytes exposed to oxidative stress and thereby enhancing its pathogenic ability (Feng et al., 2024). The study also identified the pregnane X receptor (PXR) as a key regulator of this process (Feng et al., 2024). When PXR was activated by agonists such as rifampicin (RIF) and indole-3-propionic acid (IPA), the m^{6}A modification of MALAT1 increased, while PXR knockdown led to a decrease in these methylation levels (Feng et al., 2024). Under conditions of deoxynivalenol (DON)-induced oxidative stress, researchers observed elevated m^{6}A marks at specific sites within MALAT1, indicating that environmental or chemical stressors can further enhance this modification (Feng et al., 2024). As a result, methylated MALAT1 becomes more stable and transcriptionally active, contributing to hepatocyte injury, oxidative imbalance, and weakened antioxidant responses (Feng et al., 2024). Collectively, these findings suggest that m^{6}A methylation functions as a stress-responsive mechanism that strengthens MALAT1's pathogenic role in liver disease (Feng et al., 2024).

M^{6}A Modification as an Upstream Driver of MALAT1 Activity

Together, these studies reveal that m^{6}A modification is a central post-transcriptional mechanism that reinforces MALAT1 expression, stability, and disease-promoting function (Shu et al., 2021; Feng et al., 2024). In liver fibrosis, METTL3-driven methylation promotes inflammatory activation in macrophages, while under oxidative stress, YTHDC1 and PXR signaling maintain MALAT1 stability in hepatocytes (Shu et al., 2021; Feng et al., 2024). Understanding this regulatory relationship provides new insights into the epigenetic control of liver pathology and highlights potential therapeutic opportunities for targeting the m^{6}A machinery to modulate MALAT1 activity.

The MALAT1–EZH2 Axis and Gene Silencing

MALAT1 Recruitment of EZH2 to Silence Protective Genes

EZH2 (Enhancer of Zeste Homolog 2) is the catalytic subunit of the Polycomb Repressive Complex 2 (PRC2), which deposits trimethylation at histone H3 lysine 27 (H3K27me3) to silence gene transcription (Chen, Kang, et al., 2022). In liver pathology, MALAT1 uses EZH2 as an epigenetic regulator to repress genes that normally protect hepatocytes from injury, inflammation, or apoptosis (Chen, Kang, et al., 2022). Through direct interaction with EZH2, MALAT1 alters chromatin states at specific promoters, suppressing beneficial regulators of regeneration while enabling signaling pathways that drive fibrosis, oxidative damage, and cellular dysfunction (Chen, Kang, et al., 2022). Thus, EZH2 acts as a central mediator through which MALAT1 establishes pathogenic transcriptional programs across multiple liver diseases. (Chen, Kang, et al., 2022).

The MALAT1/EZH2/GFER Axis

Recent evidence shows that MALAT1 directly recruits EZH2 to repress GFER, a gene essential for hepatocyte survival and mitochondrial homeostasis during ALI (Chen, Kang, et al., 2022). Global genomic screenings in healthy mouse liver tissue have confirmed MALAT1 as one of the EZH2-binding lncRNAs present in liver tissue (Wang et al., 2018). In both ALI patient samples and LPS-induced hepatocyte injury models, elevated MALAT1 levels correspond with decreased GFER expression, leading to enhanced H3K27me3 enrichment at the GFER promoter and transcriptional repression (Chen, Kang, et al., 2022). This epigenetic repression mechanism severely curbed hepatocyte proliferation, exacerbated cellular apoptosis and oxidative stress injury, and ultimately aggravated clinical outcomes associated with ALI (Chen, Kang, et al., 2022). Collectively, these findings establish that the epigenetic interaction between lncRNA MALAT1 and the methyltransferase EZH2, which forms the MALAT1/EZH2/GFER axis. This key mechanism drives hepatocyte dysfunction, the advancement of ALI by epigenetically suppressing GFER and, subsequently, the activation of the AMPK/mTOR signaling pathway, amplifying metabolic stress and further damaging hepatocytes (Chen, Kang, et al., 2022). Beyond acute injury, the MALAT1–EZH2 axis is also implicated in hepatocellular carcinoma (HCC), where high EZH2 expression correlates with poor prognosis and promotes immune evasion through upregulation of checkpoint markers such as PD-L1 and CTLA-4 (Chen, Lin, et al., 2022). Together, these findings illustrate that the MALAT1–EZH2 interaction establishes an epigenetic program that compromises hepatocyte function and resilience, contributing to both liver injury and cancer progression (Chen, Kang, et al., 2022; Wang et al., 2018; Chen, Lin, et al., 2022).

MALAT1's Disruption of Protective MicroRNAs

MALAT1-Mediated MicroRNA Dysregulation

MALAT1 drives the progression of liver pathology primarily by disrupting microRNA-based gene regulation through dual mechanisms: acting as a competing endogenous RNA (ceRNA) and regulating microRNA gene transcription itself (Xiang et al., 2022; Chen, Kang, et al., 2022). As a ceRNA, MALAT1 sequesters specific protective microRNAs, most notably miR-206, which in healthy conditions, functions to suppress lipogenesis and prevent hepatosteatosis (Wu et al., 2017). This sequestration relieves miR-206's inhibition on the ARNT transcription factor, leading to increased its expression (Xiang et al., 2022). ARNT (Aryl Hydrocarbon Receptor Nuclear Translocator) is a crucial transcription factor in the liver, serving as an essential component of signaling receptor complexes that regulate gene expression programs vital for metabolic balance and detoxification pathways (Xiang et al., 2022). The increased

expression of ARNT subsequently activates downstream genes responsible for fatty-acid uptake and lipid production, thereby exacerbating metabolic imbalance in hepatocytes (Xiang et al., 2022). Regarding transcriptional control, MALAT1 also employs its interaction with the histone methyltransferase EZH2 to exert epigenetic silencing on microRNA genes. For example, MALAT1 is established to recruit EZH2 to mainly miR-22 promoter regions, leading to the deposition of the repressive mark H3K27me3 and subsequent transcriptional silencing (Chen et al., 2020). This multi-level dysregulation of microRNA activity intensifies liver injury, complementing the direct repression of regenerative genes, such as GFER, which is also mediated by the MALAT1/EZH2 axis during acute injury (Chen, Kang, et al., 2022). Together, these mechanisms show that MALAT1 disrupts microRNA-based regulation at multiple levels, intensifying liver injury through metabolic imbalance, impaired regeneration, and increased cellular stress.

The MALAT1/miR-206 Axis

A major example of MALAT1's ceRNA activity is its interaction with miR-206, a microRNA known to protect the liver by suppressing lipid and glucose synthesis (Wu et al., 2017). Xiang et al. (2022) used both FFA-treated hepatocyte cell lines and high-fat diet mice to induced NAFLD pathology and showed that MALAT1 sponges miR-206, leading to increased ARNT expression and enhanced lipid accumulation in vitro and in vivo.Importantly, reducing miR-206 partially reverses the beneficial effects of MALAT1 knockdown, confirming that MALAT1 promotes ARNT activity by directly sponging miR-206 (Xiang et al., 2022). This interaction has consequences for diet-induced fatty liver, as inhibition of miR-206 reverses the reduced lipid accumulation observed when MALAT1 is suppressed, indicating that MALAT1-mediated inhibition of miR-206 is a key driver of hepatic lipid buildup (Xiang et al., 2022; Wu et al., 2017). By disrupting miR-206's normal metabolic regulatory role, MALAT1 contributes to fatty liver–related injury, metabolic stress, and hepatocyte dysfunction, further highlighting its central role in promoting liver disease progression Xiang et al., 2022; Wu et al., 2017).

MALAT1's Sequestration of miR-22

In addition, MALAT1 contributes significantly to the progression of liver disease by functionally suppressing the protective microRNA miR-22 through a ceRNA mechanism (Chen et al., 2020). MALAT1 acts as a molecular sponge, directly binding and sequestering miR-22. Since miR-22 normally functions as a potent tumor suppressor, guarding against unchecked cell proliferation and stress induced death, its sequestration by MALAT1 alleviates its inhibitory control over critical downstream target genes (Chen et al., 2020). A central set of these targets includes the Inhibitor of Apoptosis Proteins (IAPs), which are master regulators of programmed cell death; by suppressing miR-22, MALAT1 leads to the aberrant upregulation of IAPs, which effectively blocks the cell's natural apoptotic machinery and dramatically enhances cell growth and viability (Chen et al., 2020). This specific molecular disruption creates an environment that favors uncontrolled hepatocyte proliferation and resistance to death signals, fundamentally shifting the cell state toward malignancy and accelerating the advancement of liver pathology (Chen et al., 2020).

Conclusion

Liver disease continues to be a major global health burden, causing around 2 million deaths per year globally (Cleveland Clinic, 2023). Across specific disease contexts, including NAFLD/NASH, viral hepatitis, and hepatocellular carcinoma, MALAT1 consistently appears upregulated and functionally active.This review established the central argument that MALAT1 drives liver disease progression through its interactions with microRNAs and EZH2, and through m^6A modifications that enhance its stability and activity, ultimately disrupting protective regulatory networks and promoting metabolic, inflammatory, and fibrotic dysfunction. The collective findings revealed three major mechanistic themes. First, m^6A methylation acts upstream to enhance the stability and abundance of MALAT1, with enzymes such as METTL3 and readers like YTHDC1 amplifying its inflammatory effects (Shu et al., 2021; Feng et al., 2024). Second, MALAT1 promotes liver injury by recruiting the histone-modifying enzyme EZH2 to silence protective genes through H3K27me3 enrichment, thereby weakening mitochondrial stability and blocking hepatocyte regeneration (Chen, Kang, et al., 2022). Finally, MALAT1 intensifies damage by disrupting protective microRNAs, primarily miR-206 and miR-22, by serving as a competing endogenous RNA that worsens metabolic imbalance and overall hepatocyte vulnerability (Chen et al., 2020; Xiang et al., 2022).

Therapeutic options remain limited for liver disease. Therefore understanding MALAT1 is critically important because it actively contributes to critical pathological processes, including inflammation, fibrosis, metabolic dysfunction, and impaired regeneration, which drive disease progression (Chen, Kang, et al., 2022; Xiang et al., 2022). By examining the roles of m^6A modifications, microRNAs (such as miR-206 and miR-22), and EZH2 in controlling MALAT1 activity, this study identifies specific molecular mechanisms that could serve as potential targets for therapeutic intervention (Chen, Kang, et al., 2022; Xiang et al., 2022). Targeting MALAT1 or its upstream regulators could potentially reduce hepatic inflammation, limit fibrosis, and restore normal hepatocyte function, offering a promising strategy to treat or slow the progression of liver disease.

Despite the valuable insights gained regarding the regulatory role of MALAT1 in liver disease, the generalizability and translational success of these findings are subject to several critical limitations. Foremost among these is the reliance on mouse models, which, despite their utility, possess fundamental physiological and metabolic differences from humans. Additionally, much of the mechanistic evidence for MALAT1's function comes from isolated cell lines exposed to lipid or inflammatory stressors, which may not fully recapitulate the complexity of human liver pathology. Evidence related to key mediators, such as METTL3, YTHDC1, EZH2, miR-206, and miR-22, is also largely derived from in vitro or early preclinical systems, leaving uncertainty about how these interactions behave across diverse disease stages, comorbidities, or patient populations. These limitations highlight the need for more translational models and human-tissue validation.

The research demonstrates the substantial regulatory influence of MALAT1 across multiple forms of liver disease, and despite the noted limitations, the collective findings point to a clear need for continued, in-depth investigation into this lncRNA due to its significant role in driving disease progression. In particular, the role of EZH2 (Enhancer of Zeste Homolog 2) within this pathway deserves focused research attention. Because the EZH2 interaction represents a mechanistic insight that remains insufficiently explored in the literature, its further validation and detailed characterization are essential steps toward identifying novel and clinically meaningful therapeutic targets in liver disease.

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Virophage, Giant Viruses, and their Potential Anti-Viral Applications

Sebastian Gadala-Maria

Abstract: Virophages are a new type of virus, having the unique ability to parasitize giant viruses by preventing their reproduction (Tokarz-Deptuła et al., 2023). Virophages cannot reproduce virophage particles without a host cell that has already been infected with a giant virus, such that the giant virus has already created its viral factory which is hijacked by the virophage (Tokarz-Deptuła et al., 2023; Arco & Becks, 2024). This paper discusses both the structure of virophages and the behavior of virophages in a tripartite system with the giant virus and host cell. The methodology used involves a literary analysis of many publicly available sources relevant to the study of virophages, with the aim to examine their potential to be used in certain antiviral therapies. The relationship between the rate of reproduction of both the giant virus and the virophage has been shown to be more favorable to the host cell with the virophage as opposed to without (Arco et al., 2024). Potential use cases for virophages in a future antiviral therapeutic context may be possible, noting that the recency of the discovery of virophages leaves much yet to be discovered about the nature of virophages.

Key Words: Virophage, Giant virus, Coinfection, Parasitization

Introduction

Traditionally speaking, viruses are microscopic organisms that rely on the infection of a host in order to reproduce, usually resulting in the death of the host cell (Cleveland Clinic, 2023). Physically, viruses are a small amount of genetic code inside a protective shell, known as a capsid (Cleveland Clinic, 2023). In 2003, giant viruses, viruses much larger than previously acknowledged, changed the perception of what viruses are and can be (Simón et al., 2024). In 2008, Virophages were discovered (Bekliz et al., 2016). Virophages are much smaller than typical viruses and cannot reproduce without the prior infection of a host cell by a giant virus (Bekliz et al., 2016). Due to their unique parasitic nature, virophages show potential as a method of treatment via suppression of viral reproduction in the future. The aim of this paper is to use currently available information in order to discern the viability of the use of virophages in anti-viral therapy by analysing their structure and observed behavior. Unfortunately, due to their new discovery, there is still a lot unknown about virophages and their relationship with giant viruses. However, further inquiry into the study of virophages may prove useful according to the current body of knowledge.

Basic Structure of Virophages

Viruses typically range between 20-200nm in diameter, yet some species, such as Giant Viruses, can be as big as 2μm (Abergel & Claverie, 2020; Louten, 2016). Virophages are much smaller than typical viral pathogens, ranging from 35-74 nm in diameter (Bekliz et al., 2016). The size difference between virophages and giant viruses has been speculated to allow some species of virophages to adhere themselves to the outside of a giant virus or endocytose into a giant virus particle, thus assisting in reproduction of the virophage (Tokarz-Deptuła et al., 2023). Virophages are non-enveloped (lacking a lipid/fat layer that would surround the capsid) viruses with icosahedral capsids (Bekliz et al., 2016). Genetically speaking, all virophages have double stranded DNA (dsDNA), which indicates their heavy reliance on the reproductive cycle of the host cell relative to other

kinds of viruses (Tokarz-Deptuła et al., 2023; Inés Colmegna & Alberts-Grill, 2009). At the moment, approximately 41 different virophage species have been discovered (Tokarz-Deptuła et al., 2023).

Among the various different species of virophages, there are a variety of genetic sequences that are found in commonality amongst many different types of virophages. Known as VpPC (Virophage Protein Clusters), these genetic sequences code for a number of different tools used by many, if not all virophages (Tokarz-Deptuła et al., 2023). VpPC_005, for example, is a phage integrase/recombinase and present in approximately 51.2% of proposed high quality (HQ) virophage genomes (Paez-Espino et al., 2019). The HQ VpPC_005 allows the virophage to fuse its own DNA with the giant virus that it's parasitizing, creating a genetic combination of the two known as a provirus (Tokarz-Deptuła et al., 2023). Notably a form of tRNA (transferable ribonucleic acid) has been seen in 7% of HQ proposed virophage genomes which, according to Paez-Espino et al. (2019), these tRNA sequences did not display high sequence similarity to any tRNAs in isolate genomes in NCBI or IMG databases, and therefore, their origins are uncertain.

Virophages Replication

One can draw a distinction amongst the currently known species of virophages based on the various, known replication cycles amongst different groups of virophages. As of the current body of knowledge, there are three modes of virophage replication: coinfection, reactivation of integrated virophage genome, and vertical transmission (Tokarz-Deptuła et al., 2023).

There are multiple ways a virophage can coinfect a cell. Coinfection is the process by which a virophage, concurrently or independently, directly hijacks the viral factory of a compatible giant virus and uses it to create virophage particles inside of an infected host cell (Taylor et al., 2014). The first and most well studied method of coinfection in virophages is adhesion, most notably used by Sputnik 1, (Tokarz-Deptuła et al., 2023; Taylor et al., 2014). Adhesion is a proposed method of coinfection that occurs when protrusions on the exterior of a virophage are compatible with the protrusions on the exterior of the giant virus (Desnues et al., 2012). These protrusions may allow the virophage to adhere itself to the exterior of the virus that is being parasitized (Tokarz-Deptuła et al., 2023). While adhered, the virophage is able to coinfect the host cell by riding along the virus' outer shell of the parasitized virus and then take advantage of the virus and host once both have undergone endocytosis via the host (Bekliz et al., 2016). The second method of coinfection involves the independent infection of the host cell by the virophage and the giant virus, which occurs when the virophage endocytosis' into the host cell independently from the giant virus, rather than alongside it (Taylor et al., 2014). Mavirus is the most notable virophage that uses independent infection as a method of coinfection along with its host virus (Bekliz et al., 2016). In other words, Mavirus is capable of going through endocytosis of the host cell by itself, however it cannot reproduce until the host it has already infected also gets infected with a giant virus strain, such that Mavirus is then able to hijack the viral factory and proceed with coinfection. While at this point, some virophage species may directly hijack the viral factory of a giant virus and reproduce there, Mavirus particles may not depending on the circumstance. Mavirus is capable of reproducing using the other two methods which involve transfer of DNA instead of directly taking over the viral factory (Tokarz-Deptuła et al., 2023; Arco & Becks, 2024).

Once the giant virus has endocytosed, Mavirus takes over the viral factory by inserting its DNA into the host cell. (Tokarz-Deptuła et al., 2023; Arco & Becks, 2024). Specifically, the reactivation of an integrated virophage genome in the case of Mavirus occurs as a result of the Mavirus' ability to integrate its genetic code into both the giant virus (if present) that is infecting the cell and the host cell (Tokarz-Deptuła et al., 2023). When Mavirus integrates its genetic code inside of the virus', the viral factory produces genetically altered provirophages, which are viruses that have had the genetic information of a virophage integrated into their own genetic code (Desnues, La Scola, et al., 2012). When these provirophages infect a compatible cell, there is a stochastic probability that, rather than producing more provirophages in the viral factory, the viral factory will produce the virophage, in which case, Mavirus particles would be produced instead of the giant virus' virions (Arco & Becks, 2024; Bouchard et al., 2025).

Vertical transmission occurs when the genetic information of a virophage is integrated into the host cell (Mónica Berjón-Otero et al., 2019). Once the host cell undergoes replication, the genetic information of the virophage is present in the genome of the new generation of the host (Blanc et al., 2015). Similar to reactivation, it does not involve creating virion particles then and there. Instead, vertical transmission involves replication via the transfer of the genetic code required to replicate the virophage via the replication of the host's genome. When that genetically altered host is infected with a viable giant virus, the virophage's code is activated inside of the viral factory, resulting in the replication of virophages instead of the giant virus (Mónica Berjón-Otero et al., 2019; Tokarz-Deptuła et al., 2023).

The importance of the distinction among the three methods of virophage genetic replication involve the transposing of the virophage genome onto the host's genome. If virophages were to ever be used in anti-viral therapy in humans, the method of replication of the virophage particles would likely be coinfection, rather than reactivation or vertical transmission, to avoid the possibility of the virophage genome integrating itself into human cells and the many consequences that might have.

What is a Giant Virus?

Giant viruses are also a relatively recent discovery, though slightly less recent than virophages (Simón et al., 2024; Tokarz-Deptuła et al., 2024). Giant viruses are very large viruses with relatively complex genomes for a virus (Abergel & Claverie, 2020; Simón et al., 2024). These viruses belong to the family Mimivire and the phylum Nucleocytoviricota, which shares a set of genes related to structural and replication modules (Tokarz-Deptuła et al., 2023). Their large size and genome allow them to possess many interesting abilities which a normal virus might not be able to, and is part of the reason virophages are able to find space to adhere to the surface of a giant virus (Tokarz-Deptuła et al., 2024). Notably, different virophages interact with giant viruses differently depending on the

circumstance. Various factors (such as, but not limited to, species of the giant virus, population, genetic variant of the virophage) can influence the rate of reproduction of the virophage (Arco et al., 2024; Tokarz-Deptuła et al., 2024). Likewise, a virophage must be compatible with that species of giant virus in order to reproduce in the first place (Tokarz-Deptuła et al., 2024). As far as this paper is concerned, the broad relationship between giant viruses and virophages have a few distinct and relevant properties when proposing the possibility of using virophages in the context of antiviral therapy: the dynamic of reproduction amongst virophages and giant viruses, defences used by giant viruses in order to combat the parasitization of virophages, and how virophages benefit the host cell more than their absence.

Giant Virus and Virophage Replication Dynamics

Since virophages need to lyse and interrupt the replication of giant viruses in order to reproduce, while also not driving giant viruses to extinction within that system, virophages must maintain a balance between reproduction and over consumption the population of giant viruses (Arco et al., 2024). As a result, the rate at which virophages reproduce has been shown to decrease over time in an isolated system such that they do not eradicate their source of reproduction (Arco et al., 2024). Likewise, should the quantity of giant virus particles increase, it will also increase the probability that a virophage coinfects with a giant virus/activates an integrated virophage genome in an infected host cell (simply because there is a higher chance of the different particles coming into contact with each other). Importantly, since a hijacked viral factory produces little-to-no giant virus particles, virophage infection will result in more virophages being reproduced before host lysis than giant viruses (Tokarz-Deptuła et al., 2023; Arco et al., 2024). Thus, there has to be a delicate balance established between giant virus replication and virophage replication such that neither reproduce to the point of overwhelming the population growth of the other (Arco et al., 2024). This oppressive relationship on the part of the virophage is what makes it parasitic (Tokarz-Deptuła et al., 2023).

Giant Virus Defence Against Virophages

Some giant viruses have miraculously evolved defence systems in order to combat virophage coinfection (Bekliz et al., 2016). MIMIVIRE (MIMIvirus VIrophage Resistant Element) is the best recorded example of a virophage defence system in a giant virus (Bekliz et al., 2016). CRISPR-Cas-like system of defence discovered in a specific lineage of mimiviruses that has been demonstrated to provide that lineage with a unique resistance and immunity to infection from Zamilion virophage parasitisation (Bekliz et al., 2016). In particular, a 28-nucleotide-long sequence in the Zamilian genome was discovered to be identical to a sequence present a certain lineage of mimiviruses (another name for giant viruses) along with another 15-nucleotide-long sequence repeated 4 times, with a common correlation amongst this lineage being their noted resistance to the Zamilion virophage (Bekliz et al., 2016). The second sequence was predicted to encode for proteins with helicase and nuclease functions that seemed to be involved in certain nucleic acids, which was later validated experimentally (Bekliz et al., 2016). The system was thus described with the unique ability to identify a specific sequence of genetic code and then target and dissolve that code such that it would no longer function (Bekliz et al., 2016). There are differences between MIMIVIRE and CRISPR-Cas, such as the necessity of MIMIVIRE's integration into the host's genome before it can be put to any use (Bekliz et al., 2016). Since giant viruses, virophages, and their behavior are such a new discovery, there may be other defence systems that have yet to be discovered or lack accessible documentation, so this is likely not the only system used by giant viruses against giant viruses.

How Virophage Disruption of Giant Virus Replication Benefits the Host Cell in a System

The dynamic between just virophages and the giant viruses itself is already very delicate, but they also need to manage the replication of the host cell in such a way as to not eliminate their host. Since both the virophage and the giant virus rely on the lysis of a host cell in order to reproduce, it becomes evident that this tripartite system is very easy to disrupt and manage properly (Arco et al., 2024). However, since a virophage cannot reproduce without the initial infection of a giant virus, such that the giant virus creates a viral factory, and thus, cannot cause lysis of a host cell that the giant virus has not already infected. The addition of the virophage can only then disrupt the replication of the giant virus, such that it (at the very least) slows the rate of infection within that given isolated system (Arco et al., 2024).

Disruption of Balance to Work With an Immune System

Virophages have already been demonstrated to weaken the rate of infection of giant viruses in a given system such that the host cell population is not as hindered as it would be without a compatible virophage in the system (Arco et al., 2024). Thus, given a compatible giant virus, and the lack of an immune response targeting the virophages themselves, virophages could, hypothetically, be used to further weaken the infection of the giant virus and simply assist that immune system by hindering the virus's ability to reproduce. Importantly, since virophages cannot cause lysis in a cell without that cell already being infected by a giant virus, the resulting effect of introducing virophages into an infected organism should, assuming all goes well, only decrease the number of casualties in the afflicted organism by preventing the reproduction of the giant virus while the immune system deals with the infection.

Depending on the immune response, virophages may be able to provide resistance to future infections as well simply by remaining inside the organism of the host. This, of course, relies on the hope that the immune system does not consider virophages to be a threat, which is another very possible scenario. If that were to be the case, then the symptoms may vary from something similar to an allergic reaction in which the immune system seeks to destroy all virophage particles, although that is pure speculation. Granted, since virophages alone cannot cause lysis, and they have been observed to (at least) slow down the rate of reproduction of the giant virus, it may still be worth it in that scenario to introduce a compatible virophage into the system. Doing so, hypothetically, could allow the host more time to fight back against the actual threat (the viral infection of the giant virus) and, once done, let the immune system remove the virophage particles quickly (they cannot reproduce without the

infection, so the virophage particles themselves would much easier to get rid of than the giant virus particles).

Overwhelming the Giant Virus Reproductive Cycle in a Tripartite System

Since the virophage-virus relationship inside the tripartite system has been observed to try and balance their reproduction rates such that neither outconsumes the other, virophages on their own do not seem to be capable of completely preventing the reproduction of the Giant virus on their own (Tokarz-Deptuła et al., 2023). The balance of virophage and viral results in the virophage reproducing less in order to prevent the over parasitization of the giant virus, which is necessary for the virophage to reproduce. However, the balance seems to be dependent on the population of the host, virus, and virophage inside the system relative to each other (Arco et al., 2024).

Current Issues With Virophage Therapy

One potential issue with this approach may be the possibility of an immune response resulting from the virophage particles themselves, in which the immune system attacks them, similar to an allergy response (John Hopkins Medicine, 2019). While it very well could be an immune response similar to an allergic reaction, there is so much that is still unknown about virophages that saying so is more of an assumption than I would be comfortable with.

The main issue with the use of virophages in an anti-viral therapy setting is simply the lack of field-specific research. There is only so much one can observe with such a small amount of data before it starts to lean closer to speculation rather than reality. That being said, the potential for virophages to be used in such a setting is not completely impossible either, and may prove valuable in the future when more research has been done.

Conclusion

In short, virophages and their relationship with both giant viruses and their respective host cell are a new and rapidly progressing field of study. Virophages, being relatively small viruses which are incapable of reproducing viral particles inside a host cell without the use of the giant virus' viral factory, have been shown to inhibit the reproduction of the giant virus with which it is coinfection the host cell (Bekliz et al., 2016). There are three different ways in which virophages can reproduce their genetic information, each belonging to different sets of virophages and resulting in different rates of reproduction. The three methods of reproduction are as follows: coinfection, reactivation of an integrated virophage genome, and vertical transmission (Tokarz-Deptuła et al., 2023; Auer et al., 2024). The tripartite system by nature involves the eventual reduction in infectivity of the giant virus and the slowing down of the rate of infection in the tripartite system as a whole.

Very interestingly, the tripartite system of virophage, giant virus, and host cell will try to adjust and maintain a homeostasis, resulting in a longer lifetime than a similar system excluding the virophage (Arco et al., 2024). This occurs as a result of selection on the part of both the virus and virophage, in which the virophage cannot reproduce so rapidly that it hijacks more giant virus viral factories than are being produced (which would lead to extinction of the virus and the virophage) and the virus cannot reproduce more rapidly without also increasing the reproduction rate of the virophage (Arco et al., 2024). Because of this tripartite relationship and its longer relative life than that of the giant virus and host cell, in combination with the apparent inability for a virophage to reproduce without the presence of the virus, it has been proposed that virophages may prove useful in anti-viral therapy (Mohan et al., 2024).

While at the moment, due to the lack of general information as a result of the recency of this discovery, the availability of known virophages is very miniscule, with there having been only being 41 discovered virophages as of 2023 (Tokarz-Deptuła et al., 2023). Thus, while the viability of virophages in anti-viral therapy is rather promising, there are relatively few virophages to draw from, meaning there are likely very few compatible, available, and useful tripartite groups that are viable for usage in anti-viral systems.

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fMRI-Based Deception Detection and Forensic Validity

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Abstract: Functional magnetic resonance imaging (fMRI) has been proposed as a tool for detecting deception by identifying neural activation patterns rather than skewed observable behaviors. Despite fMRI's ability to map cognitive activity, deception is a complex social process that often has confounding signals that it shares with other social phenomena, such as arousal; this makes fMRI validity in a forensic setting highly contested. This study aims to identify how fMRI can be enhanced to more reliably detect deception and evaluate a forensic application. Through comparing fMRI deception detection studies, a structured review of task paradigms' validity, neural regions implicated, and experimental controls was conducted. Importance is placed on studies containing neuropredictive models and those testing applicability to forensic scenarios. Throughout the reviewed research, brain regions associated with executive functioning and truth suppression, like the anterior cingulate cortex and frontal gyrus, consistently inhibited the prediction power of deception. Predictive models that counterbalanced overgeneralization, using dual-goal tuning, fostered moderate success, though results were sensitive to task design and context-dependent variables. Meta-analytical findings on fMRI task-design indicated that tasks with higher ecological validity–tasks which incorporated motivation, social interaction, and intentional deception–reduced confounding signals from other social processes and activated more specific neural networks. Overall, findings suggest the direction of further advancement should be on enhancing fMRI task design and predictive models rather than discovering a single deceptive-specific receptor. Current fMRI approaches remain unsuitable for direct forensic application, but continued methodological improvement could support future investigative practices.

Key Words: Virophage, Giant virus, Coinfection, Parasitization

Introduction

Deception is a cognitive process and social-interaction where information is intentionally manipulated (DePaulo, 2003). Traditional research of deception focused on observable behaviours such as facial expressions, fidgeting, physiological responses, etc. This research assumes that individuals exhibit certain observable behaviours when they are in the act of deception; in turn, assuming that it could be observed by a third party. This earlier line of research aimed to identify certain behavioural cues to deception; hesitation, nervousness, pauses in speech, sweating, and fidgeting were some of them. Formulating lies was thought to cause pauses in speech and hesitations, as to come up with or change a story; nervousness and fidgeting were viewed to be signs of an affliction caused by deception. Law enforcement used these behavioural cues to easily identify deception without special equipment. This can be tied to historical reliance on interrogation and pure intuition, instead of true proof. These assumptions, even used by governments, had little to no empirical evidence, but persisted due to a conflated understanding of this cognitive process and widespread misconception of true deception detection research (Opancina et al., 2024).

Throughout the test of time, there have been many claims of certain methods that truly are able to discover deception. These methods have been found to be outdated and inconsistent; there is an especially large gap between long-standing beliefs about deception (behavioural observation) and what empirical evidence actually shows. Deception in the human body is fundamentally a cognitive process involving executive functioning and inhibitory response. To measure such an activity, internal mechanisms should be used over external signs. This paper examines whether fMRI and other neuroimaging predictors will provide a more valid methodology for detecting deception than traditional means. Using fMRIs is key to finding the specific neural mechanisms activated during deception and their consistency among studies. It is intended to be an evaluation of fMRI, rather than an absolute way to detect deception.

Throughout human history, deception has been a recurring topic of inquiry; however, it remains poorly understood. As it stands right now, modern technology could be leveraged to truly grasp this complexity, allowing deception to be studied on a neural level. Inspecting deception in this capacity will contribute to an understanding of other parts of the brain, like executive functioning. Inaccurate ways of deception detection have led to serious consequences, such as law enforcement using incorrect techniques, leading to wrongful convictions. This paper seeks to

test the validity of fMRIs and neuropredictors, a possible stepping stone of deception detection, based on empirical evidence. By examining behavioural and neuroscience findings, this paper aims to identify the true capabilities and limitations of deception detection research.

Literature Characterization

Past Research & Methods of Deception Detection

Cues to Deception (2003), a meta-analysis by DePaulo and colleagues, asks whether people behave differently when they are lying compared to truth-telling. DePaulo and colleagues tested 1,338 estimates of 158 behavioural cues to deception. DePaulo and colleagues also factored in motives like monetary, transgressions, and personal gain. Among these many cues and motives, she found deception to be a very complex and unique process, which made behavioural cues have weak correlations with deception. DePaulo and colleagues found some strong truth-telling correlations between their studies, like cooperative attitudes, genuine smiles, and repetition. The research concluded that the limited number of participants may constrain the real correlations. DePaulo and colleagues rule out behavioural cues of deception and traditional deception detection, narrowing focus towards physiological responses (DePaulo et al., 2003). A major strength of DePaulo et al.'s analysis remains within its scale (1338 cues), allowing for a critical view of long-standing assumptions to be reliable and upheld in high-consequences settings like law enforcement. This study concedes pure human observation, a widely imposed method of identification, as false; this allows the examination of deception to shift to a neural-based procedure.

Throughout the judicial system, many methods of deception detection were used to sentence individuals on trial; one such technique was the polygraph. Polygraphs measure heart rate and skin conductance, synonymous with emotional arousal, not so much deception itself. Polygraphs are not entirely inaccurate as arousal and deception share many confounding signals in the brain, however they may correlate in some areas, but individuals often get false results for being truthful but anxious or trained deceptors. Polygraphs are inadmissible in court as they cannot fully identify deception, thus ruling out polygraphs in continuing deception detection research (National Research Council, 2003).

Plausible Methods of Deception Detection

An article by Opancina and colleagues reviews how advanced neuroimaging techniques might support lie detection in criminal interrogations. The researchers critique previous technology, like polygraphs, as they measure someone's anxiety or arousal rather than deceptiveness. Researchers analyze many methods of neuroimaging–Electroencephalography, fMRI, functional near-infrared spectroscopy, positron emission tomography, and single-photon emission computed tomography. FMRI is highlighted among this group as it measures changes in blood oxygen levels during neural activity with the highest resolution. Researchers cite previous fMRI studies have already pointed out which parts of the brain are used during deception, allowing law enforcement to create differentiated images of truth-telling and deception from brain scans. Opancina and colleagues say this method is limited by confounded signals and other social processes that trigger such parts of the brain (Opancina et al., 2024). This paper directs our approach to fMRIs as they have already been tested in use for detecting deception, as they are also conveyed, by Opancina and colleagues, to have the potential for enhancement.

FMRI as a Use of Deception Detection

Deception is a cognitive process, and as being such, the analysis of deception should involve brain imaging. Brain-based measures can view the foundational brain activity of deception among humans. Distinct from behavioural cues, analyzing deception cognitively could find the commonality of deception in human biology. Neuroprediction shifts research to ask what the brain does during deception, rather than what deception looks like.

Functional magnetic resonance imaging (fMRI) is a method of neuro-prediction, as it detects changes in blood flow and oxygenation–helping to map brain activity. FMRIs identify specific brain regions/receptors activated during certain cognitive processes, activities, and emotions. Deception, a cognitive process, consistently inhibits distinguishable activity from truth-telling in specific brain regions. These regions include the angular gyrus and inferior frontal gyrus. Each of these regions' functions plays a specific role in deception. The angular gyrus (AG), responsible for processing and retrieving knowledge, helps discern truthful and deceptive responses as this section processes the two activities as completely different. The inferior frontal gyrus (IFG) plays a key role in truth suppression. The IFG is important in predictive lying as greater activation means greater truth suppression, which identifies if someone is lying and reveals how skilled they are at deception (Feng et al., 2022). This allows deception to be defined in these regions, narrowing the fMRI analysis of deception in the brain. Feng and colleagues articulate what each of the sections does in relation to deception, which remains important for mapping different types of deception (distortions, half-truths, untruths), as this may create different activity configurations of these core regions. These implications are critical to the development of the application in forensic and investigative work.

Dual-Goal Tuning is a method/algorithm proposed by Lee and colleagues, which is said to possibly differentiate between deception and other social processes in the brain (Lee et. al., 2024). Dual-goal tuning starts by looking at specific brain regions such as the dorsal anterior cingulate cortex and superior frontal gyrus, which are known to possess predictive power (Lee, 2024). Dual-Goal tuning is proposed as a building block to a forensic application, as it tries to enhance fMRI usage by removing generalizing the area of analysis, whilst trying not to overgeneralize deception and other social processes.

With the understanding that dual-goal tuning seeks to enhance fMRI data, in a pre-print article led by researcher Sangil Lee tests the neuroreceptors related to deception using fMRI and dual-goal tuning. Lee and colleagues create a paradigm that promotes distinction of confounding signals, to not confuse deception with selfishness. This task involves deception trials and non-deception trials, where participants could either lie to another person for benefit, or be forced to engage in non-deceptive, selfish choices for self-benefit. In subject-level prediction–each subject had two discernible images, one of truthfulness and one of deception–they

found the methods to be 78.8% accurate. In trial-level prediction–estimated created by algorithms–the predictors still performed above chance at 56.6%. The imperfect results can be attributed to the remaining presence of confounding signals. The researchers add that one formed neural predictor for a certain deceptive situation may be less accurate in another deceptive situation. Lee and colleagues view the results as promising, as certain constructs can be built for certain deceptive behavior (Lee et. al., 2024). Overgeneralization (of confounding signals) is a limitation, as it "lacks discriminant validity," as the high accuracy does not mean the system is only detecting deception, but instead identifying selfishness in truth-tellers. Overall, the article provides a path to the goal of deception detection, with work still needing to be done, stating that tests with new limitations must be done, with improved dual-goal tuning. Although this version of the study was not peer-reviewed, the analysis remains imperative in understanding the abilities that predictive models like dual-goal tuning should demonstrate.

Another study, also led by researcher Sangil Lee, tests the accuracy of functional MRI-based neural prediction using dual-goal tuning to detect deception. Lee and colleagues use the results from their pre-print study to assess the validity problem of neuroimaging. From this data, they confirm that instead of overgeneralizing, their model actively discriminates deception from a closely matched non-deceptive behavior (Lee et al., 2024). This peer-reviewed article highlights how dual-goal tuning can be used, even in a very harshly paired environment (deceptive v. selfishness greed task), to detect deception. Lee and colleagues propose another method, identifying a specific deceptive receptor, which would be easily distinguishable, but ultimately may not exist. The work in fMRI and dual-goal tuning is promising, but there is still research to be done. Plausible application in the field of forensics is foreseeable in the future, as the quest to detect deception is ongoing, and is necessary for this line of work.

Although dual-goal tuning is a feasible method of deception detection, Delgado-Herrera and colleagues evaluate how task designs–similar to Lee and colleagues' work–affect fMRI findings in deception detection. During their analysis of 59 contrasts, researchers found that high ecological validity tasks–tasks that included intention to lie, social interactions, and motivation– were more realistic and, more importantly, narrowed down the neural regions activated in the act of deception. Delgado et. al. found that higher ecological tasks recruited the right insular cortex and bilateral anterior cingulate cortex, suggesting that more natural deception engages more specific neural networks rather than confounding signals (Delgado-Herrera, 2021). Identifying high ecological validity tasks that create realistic settings is a key finding, as it will help develop a functional MRI role in deception detection in real-life forensic applications. This discovery also helps evaluate previous studies' design tasks, which could be enhanced with a high ecological validity design.

Across this review, deception constantly emerges as a fundamentally cognitive process, therefore cognitive-based methods are most appropriate for identifying the specific neural configuration of deception. Foundational neuroimaging data show that the angular gyrus and the inferior frontal gyrus are consistently engaged during deceptive responses, supporting the claim that truth suppression and information manipulation are involved in lying. From this foundation, predictive validity enhancement like dual-goal tuning represents a methodological advancement, as the shift focuses towards improving the validity of fMRI's ability to detect deception by distinguishing between other closely related social processes.

The work of Lee and colleagues acknowledges the promise and limitations of this approach. Dual-goal tuning seeks to improve the discriminant validity by eliminating overgeneralization; accuracy remains context-dependent, reinforcing concerns about task design. This fact is further acclaimed by Delgado-Herrera and colleagues, whose findings demonstrate that higher ecological validity tasks activate more specific and realistic neural networks involved in deception. Overall, these studies suggest that the future of fMRI deception detection does not lie in a specific neural marker, but in carefully-designed, context-specific paradigms that minimize confounding signals and preserve real-world relevance. At this time, current methods are not yet suitable for direct forensic application; however, with continued enhancement in task-design, predictive modeling, and ecological validity, the prospect of neuroprediction-informed deception detection is increasingly possible.

Deception Detection Technology in Forensics

Forensics is the application of scientific methods and techniques to investigate crime and gather evidence, or to find anything suitable for legal proceedings. Crime and deception intertwine through deception in testimony, suspect interviews, and offender behavior, making deception a methodologically difficult task for forensic analysts to identify. Many have tried, applying their knowledge to create methods and techniques to overcome this challenge; in China circa 1000 BCE, a legal test for deception required individuals to keep dry rice in their mouths—if the rice remained dry after being expelled, the person was judged to be lying. This method was conceived because anxiety and nervousness, believed to be tied to deception, were thought to reduce salivation (Vicianova, 2015). In the 1920s, criminologists invented the polygraph, which tracked respiratory rate, blood pressure changes, and skin reactivity. This machine focused on capturing the subtle physiological changes during deception. Technological advancements have enabled forensic analysts to create more accurate techniques to solve crimes and detect deception. Modern neuroscience technology, like fMRI, allows scientists to capitalize by examining the patterns of activation in the brain linked to deceptive processes. The growth of knowledge permits the development of new methodologies to most accurately detect deception, investigate, gather evidence, and enhance forensic decision-making.

FMRI detection of deception has not yet been labeled as a used and working method in the field of forensics. For this reason, Kozel and colleagues formulated a task design with very high ecological validity, using a "mock sabotage crime paradigm" which simulated a real-life scenario. Researchers randomly assigned participants ("healthy, nonmedicated adults between the ages of 18-50 years") to two groups: a mock-crime group or a no-crime group. The mock-crime group was instructed to pick up a confidential envelope and steal and destroy a CD containing the video of a convenience store robbery, and admit to picking up the envelope, but not destroying or stealing the CD. The no-crime group did not pick up the envelope or the CD, but were told to lie

about picking up the letter. The fMRI results showed 100% sensitivity (ability to detect mock-crime group), but only 33% specificity (ability to detect no-crime group), making fMRI a means of ruling out people in deception detection (Kozel et. al., 2022). This study provides a real connection to forensics as it has a high ecological validity task and finds fMRI useful in weeding out suspects with its perfect ability to determine suspects. However, the results are limited by the approximation of their task-design, which cannot equal the level of jeopardy in real-world testing. The inclusion of fMRI's could be used as a tool to help overcome deception in a forensic study, as it could help weed out suspects, but not as a primary or complete solution.

(Could include study, but it's saying that fMRI technology makes a juror more prone to a guilty verdict because of confidence in fMRI technology despite not questioning validity– strays away as the technology should not be used if it's in a courtroom, but no technology would be 100%.)

Conclusion

For thousands of years, deception was viewed as only an observable process, yet modern knowledge and technology are able to discern this concept as being a neural process that must be analyzed through a cognitive lens. FMRI-based neuroprediction, when enhanced by methods like dual-goal tuning, shows greater, in-theory validity than traditional human-observable behavioural patterns. This is not to say fMRI usage is a definitive lie detector, but to acknowledge the valuable use and potential of neural technology in studying deception.

This review highlighted many important findings depicting the past, current, and potential future work of deception detection. DePaulo and colleagues' study demonstrates that commonly thought behavioural signals of deception really have a weak correlation, and research should look inward. Polygraphs are shown to be unreliable despite their biological approach, measuring other social processes rather than deception. This focus allows work to transition to fMRI and neuroprediction, where accuracy varies as task-design and approach control the validity. FMRI may not be ready for a forensic application, but it shows promise with high ecological validity tasks and an approach to combat overgeneralization like dual-goal tuning.

Deception is best defined as a cognitive process; therefore, to best understand deceptive behaviour, it should be viewed at a neural level. This is not to state that neuropredictors are entirely correct, however they do address scientific weaknesses in older methods. FMRI technology is not meant to replace ethics and legal judgment, as letting a brain scan decide the truth would be unethical due to its lack of acknowledgment in human comprehension or understanding of morals in the given predicament. This paper seeks to disseminate neuroscience contributions to better the understanding of executive functioning, social processes, and how the brain operates within the confines of deception research, while also evaluating fMRI and its enhancements' ability to translate to a forensic setting.

Researching a method of detecting deception is inherently flawed, as deception is not a stable neurological or psychological process, but rather a context-dependent behavior. Despite this, researchers have approached the problem using different procedures and methodological frameworks. Even within fMRI research, findings are scattered, as some may use methods like dual-goal tuning to improve overgeneralization, whereas others may not use such techniques and instead search for a deception-specific neural receptor. Across all deception research, combating confounding signals has been the main challenge of identifying deception. It is important to acknowledge the limited diversity in tasks, participant demographics, and types of deception, as most participants were younger adults and were given tasks designed to assess validity under extreme confounding signal conditions. This finite variation in studies makes a plausible forensic connection difficult. It is also important to mention that there are certain aspects of real-world settings that are not fully replicated during testing, like stress and complex circumstances. Additionally, fMRI technology is expensive and not widely accessible.

It is important that research continues on fMRI deception detection, as the work is positive and could be a useful tool in forensic settings. Thus, further research must be conducted on creating efficient task and approach design, which have high ecological validity and have a high chance of overcoming overgeneralization; refinements such as this would make fMRI more accurate and reliable, cutting down its inherent limitations.

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Targeting the MRGPRX2 Pathway in Mast Cell Activation Disease through urticaria

Juan Diego Alvarez

Introduction

Mast Cell Activation Disease is a multisystem condition that creates allergy-like symptoms for patients. People with MCAD often have to see multiple physicians to receive treatment, which can often focus on superficial treatment of specific symptoms. These symptoms include but are not limited to: migraine headaches, fatigue, brain fog, urticaria (hives), hypotension, and diarrhea, with migraine headaches being particularly severe in patients. Urticaria treatments for the skin have proven effective in recent studies, and applications of these treatments in the brain may function to prevent migraines in both MCAD patients and the general population. With further applications of proven treatments, this multisystem condition may prove less harmful for affected patients.

People are typically aware of their allergies, and can avoid specific triggers; however, patients with Mast Cell Activation Disease (MCAD) can experience constant reactions in response to a plethora of allergens [1]. In MCAD, mast cells (MCs), which are responsible for primarily releasing histamine in response to allergens, are upregulated, and cause painful symptoms in otherwise healthy individuals [1]. These symptoms are often multi-systematic, and can affect the whole body, in particular the brain through meningeal inflammation in the dura mater layer of the brain [2]. The meninges comprise the outermost protection of the brain, and blood flow to the dura, where mast cells reside, allowing for drugs to reach these cells [2,5]. Brain inflammation is associated with a multitude of conditions, such as brain fog, depression, and particularly migraine headaches [7,8].

One prevalent issue with MCAD, however, is limited awareness of the condition. There is limited medical research on this condition, despite it being significantly prevalent, with estimates suggesting that up to 17% of the population suffers from the illness [4]. One of the first steps that can be taken to address this issue is mediating the brain symptoms, some of which have been found to be caused by an activation of the MRGPRZ2 receptor pathway, located in meningeal mast cells in the dura mater [2]. This pathway works by activation through neuropeptides such as substance P, which prompts MCs to degranulate and release histamines and other pain mediators that cause irritation of sensory neurons in the brain [10, 13]. This irritation is one of the main causes of migraines, causing pain signals to increase excessively as nerves become more sensitive to common signals [7,8]. Blockage of the MRGPRZ2 receptor may be able to prevent its activation of MCs, attenuating neurological symptoms such as migraines and begin to provide an effective solution to this issue [12].

Meningeal mast cells and Neuroinflammation

Despite many studies focusing on how MRGPRZ2 affects MCs in skin conditions, emerging research has focused on its inflammatory effects in the brain [2]. Mast cells enter the brain during development by penetrating blood vessels with which they remain associated [3]. A recent post-stroke study demonstrated how MCs activated inflammation in the brain, working through the MRGPRZ2 receptor [2]. An additional study utilized MRGPRZ2-knockout mice to compare MC-induced inflammation after a stroke, demonstrating that MRGPRZ2 activates mast cells in response to stroke, in part driven by substance P [2].

Furthermore, the effects of mast cells on the brain have been heavily linked to multiple conditions, such as ASD or depression, but are particularly present in the migraine mechanism [7, 8]. According to Frontiers in Cellular Neuroscience, when trigeminal nerves release substance P, MCs release chemicals like histamine, serotonin, and cytokines, which contribute to neuroinflammation and chemically irritate trigeminal nociceptors — pain-sensing nerve endings of the trigeminal nerve [7, 8]. Irritation of these directly leads to nociceptors becoming more sensitive to normal stimuli such as blood pulsing, exaggerating pain signals [7, 8]. This may serve as an explanation for why many patients with MCAS suffer from migraines, and further focusing on this pathway could address one of the symptoms of this multi-systematic condition [7, 8].

A study additionally showed that MRGPRZ2 antagonists show promise in treating brain inflammation for stroke patients, as the location of the receptors on the meninges makes it an ideal site for drug delivery [2]. This suggests that, in theory, treatments that alleviate skin conditions by inhibiting the MRGPRZ2 degranulation pathway could mitigate brain inflammation by the same mechanism [12]. Consequently, researching functioning MRGPRZ2 antagonists' effects within the brain could be a viable route to address neuroinflammation [12].

Trigeminal Sensitization and Migraines

Due to MCAD's adverse effects on the whole body and the brain, the condition is heavily involved in certain neurological and psychological issues [15, 16, 18]. The adverse neuro-psychiatric effects of mast cell activation have been associated with depression, Autism Spectrum Disorder, Alzheimer's and Parkinson's, and migraines [15, 18]. In a 2011 study on systemic mastocytosis, 56.2% of patients reported recurrent headaches, with 37.5% meeting the diagnostic criteria for migraine [19]. MC degranulation plays a key role in the migraine mechanism by releasing vasodilators, chemicals that widen blood vessels by relaxing muscular walls, which can irritate the trigeminal nerve and contribute to multiple other neurological conditions associated with headaches [17].

This is reflected in patient data; approximately 25% of patients with systemic mastocytosis report chronic daily headaches at least 15 days per month, indicating persistent neurological symptoms [19]. This makes migraines one of the most common and debilitating symptoms that MCAD patients suffer from. Recent clinical evidence continues to solidify the link between migraines and mast cell activation disease; one study describing a similar irritation of nociceptors by MC mediators demonstrated the high prevalence of chronic migraines for MCAD patients specifically. In a sample of MCAS patients, approximately 70% of female patients and 47.4% of male patients reported migraines or severe headaches, making it one of the most common neurological symptoms in the population studied [15]. Additionally, mastocytosis patients with migraine headaches scored significantly higher than patients with similar headaches on the Headache Disability Inventory, which measures the level of impairment caused by headaches [19]. Overall, the evidence points to migraines as one of the most prevalent and detrimental symptoms for MCAD patients, due to the irritated nociceptors.

Therapeutic Translation of Targeting MRGPRZ2

To address the neurological symptoms of MCAD, treatments that have worked on urticaria, a skin rash that is a symptom of MCAD, should be further researched [12]. The MRGPRZ2 receptors in the meninges are found to cause urticaria in the skin, and this pathway can be pharmacologically blocked [12]. One treatment that has blocked this receptor includes an antagonist called PSB-172656, which competitively inhibits MRGPRZ2 activation in both mouse ortholog and human MRGPRZ2 [20]. Another treatment is shown with a non-competitive antagonist called Compound B, which prevents MC degranulation and histamine release in human skin models [12].

Additionally, a specific competitive antagonist of MRGPRZ2 called Piperine, which downregulates phosphorylation of key signaling molecules involved in MC activation, has been shown to block early and late MC activation responses [16]. In a similar mice study to Macphee, PACAP activated expression of MRGPRZ2 and caused MC activation which resulted in behavioral hypersensitivity consistent with migraine-like symptoms [17]. In the same study, mice lacking expression of the pathway showed a significant reduction in these pain-related responses [17]. Although it is not an antagonist study, its demonstration that the absence of functioning MRGPRZ2 could provide an experimental basis for antagonist treatments of MRGPRZ2 in the brain.

As mentioned previously, the presence of MCs in the meninges makes them ideal for drug delivery [2]. With further testing, utilizing experimental treatments for MRGPRZ2-mediated urticaria on meningeal mast cells via intrathecal routes could provide promise for treating migraines in MC patients [12, 15, 16].

Conclusion:

The lack of awareness about MCAD makes it one of the hardest conditions for patients to receive a diagnosis for [1, 4]. The condition is multi-systematic and disrupts the body's normal functions due to degranulation of MCs and release of mediators, particularly in the brain [1, 13]. Symptoms of this activation commonly manifest themselves in the form of migraines; MCs play a crucial role in the migraine mechanism and lead to a multitude of other symptoms associated with headaches [7, 8, 19]. Due to the wide range of effects MCAD has on patients, the condition itself presents an additional burden on patients' well-being, and addressing it can contribute a small piece to the complete solution of their symptoms [15].

Analysis of the MRGPRZ2 pathway mediated by neuropeptide substance P demonstrates how MCs cause inflammatory effects in dermatological and neurological conditions and how their effects can be prevented through mediation of the MRGPRZ2 pathway in the brain [9, 10, 12]. Meningeal mast cells prompted by the MRGPRZ2 pathway cause migraines by releasing histamines and other mediators that irritate the neurological pain-sensing trigeminal nerves [7, 8]. This leads to an exaggeration of pain signals being fired as nerves become increasingly more sensitive to common signals such as blood pulse [7, 8]. However, their location in the meninges makes them ideal for drug delivery [2, 5].

Applications of experimental treatments to the MRGPRZ2 pathway may potentially be able to block their effects in the brain, including through MRGPRZ2 antagonists [12, 15, 16, 17]. Antagonist treatments that have worked to block the pathway in experimental urticaria treatments, including Piperine, PSB-172656, and Compound B, could show promise in addressing the neurological aspect of the disease [12, 15, 16]. These can downregulate MC degranulation and directly prevent symptoms caused by this pathway, and could theoretically be administered to meningeal mast cells by intrathecal routes [2, 12]. The facility of drugs reaching the meninges through blood flow to the dura mater could allow these treatments to directly interact with mast cells and potentially mediate them [2, 5]. Despite the difficulties in treating MCAD as a multi-systematic condition, there is a chance for an effective treatment of its neuropsychiatric effects on patients through application of other treatments for the condition's symptoms on the MRGPRZ2 pathway [12, 15].

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The Role of Oxidative Stress in Parkinson's and Alzheimer's Disease

Nathaniel Chang

Abstract: Oxidative stress is implicated as a key contributor to several neurodegenerative diseases, such as Parkinson's and Alzheimer's. Oxidative stress results from an excess of reactive oxygen species that overpower antioxidant defenses. As a result, cell membrane, protein, and DNA damage ensues. Neurons are highly susceptible to oxidative stress for several reasons. Neurons utilize high metabolic rates for energy, contain significant amounts of lipids, heavily rely on mitochondria for energy production, and cannot regenerate. The changes in the balance of redox-active metals such as iron (Fe) and copper (Cu) are significant contributors to oxidative stress mediated via Fenton chemistry and the production of leading radicals. Excessive amounts of iron also play a role in mediating neuro-inflammation in the microglial cells, thereby leading to enhanced production of ROS, resulting in neuronal damage. The occurrences of oxidative stress, changes in redox-active metals, defective mitochondria, and chronic inflammation all play a role in explaining the progressive and irreversible effects of PD and its similar effect in AD. The most interesting note about all this pathology is that, unlike the aftermath of neuronal death causing PD and AD, oxidative stress and changes in redox-active metals beget disease development.

Key Words: Oxidative Stress, Copper, Iron, Parkinson's, Alzheimers, Reactive Oxygen Species

Introduction

In the pathogenesis of neurodegenerative diseases such as Parkinson's and Alzheimer's, there is an excessive amount of ROS, which are involved in the oxidation of lipids, DNA, and proteins. These are globally prevalent neurological disorders that are on the rise because of increased aging of populations. The high levels of ROS result in oxidative stress, mitochondrial dysfunction, cellular damage, and programmed cell death (apoptosis). Shared protein pathologies and some genetic links between these diseases point to a window for early diagnosis and therapies that target the underlying mechanisms of these diseases, rather than symptomatic relief. (Lévy et al., 2019.)

In cells, the redox-active Fe and Cu species partly regulate the oxidizing stress. These metals catalyze Fenton reactions generating hydroxyl radicals that are very reactive and enhance neuronal damage. In neurodegenerative diseases, there is an imbalance between the ROS production and antioxidant defenses in the brain, leading to oxidative stress.

Iron is also known to play an essential part in balancing these pathological states, considering that overactivation of redox reactions can lead to enhancing hydroxyl radicals. Antioxidants such as iron chelators minimize oxidative stress by controlling radical reactions or scavenging free radicals from the cells. Activated microglia lead to iron accumulation and ROS, thereby overexposing neurons. Consequently, overwhelming quantities of Fe and Cu in their redox states reduce the capacity of the body to counteract the effects of excessive ROS. This is especially seen in the manifestation of Parkinson's disease, which is characterized by iron overload in the substantia nigra. Thus, a full comprehension of ROS regulation would allow for more promising therapeutic prospects.

Body

Oxidative stress, a prominent pathological factor present in a group of neurodegenerative disorders, including Parkinson's Disease (PD) and Alzheimer's Disease (AD), was described by Chong et al. (2025). Oxidative stress can be defined as a state in which the generation of reactive oxidative species (ROS) progresses beyond a level at which the antioxidant potential of the brain can handle, causing long-term damage in some brain cells. ROS, composed of superoxide anion, hydrogen peroxide, and hydroxyl radicals, are naturally produced in the human body as by-products of mitochondrial respiration in the cells. Enzymes such as superoxide dismutase and catalase protect cells from harmful ROS by neutralizing them into non-radical chemical species. However, the neurons are vulnerable and susceptible to oxidative injuries as a result of their high metabolic rate, profile, and poor regenerative capacity. Lipid peroxidation leads to the disturbance of membrane integrity and functions of neurons. Oxidative injuries can cause damage to macromolecules, leading to conflict with normal signaling functions in neurons.

The neuronal cell membrane is composed of polyunsaturated fatty acids and is very susceptible to ROS. Oxidized proteins also mediate enzyme inactivation as well as pathogenic protein misfolding and aggregation in PD and AD. Mitochondrial DNA that undergoes oxidative injury experiences the generation of cognitive impairment through the impairment and replication of transcription, resulting in energy production failure. Metals/ROS play an instrumental role in neuronal injury wherein metals stimulate cellular ROS generation and overwhelm the natural cellular damage defense mechanisms of neurons. Oxidative stress maintains a positive feedback cycle whereby ROS stimulates the occurrence of several other cellular reactions that result in increased production of ROS. This includes dysfunctional mitochondria producing more ROS that subsequently enhances neuronal injury. The production of ROS stimulated by metals

within the cell is the main contributor of injury to the neuron that eventually results in regional susceptibility of neurodegenerative diseases. Oxidative damage is also self-propagating, which is responsible for the progressive and irreversible nature of neurodegenerative diseases.

The metal ions of iron and copper are major factors involved in oxidative stress due to their redox chemistry. Once Fenton reactions are upregulated, iron and copper stimulate the reaction of hydrogen peroxide to hydroxyl radicals, which is a potent and damaging form of ROS. For example, in the context of neurodegenerative diseases, iron has been found to show a persistent and significant increase in specific brain regions such as substantia nigra of PD, hippocampus and cortex of AD (Chen et al., 2025).

Apart from the oxidative damage itself, another important role of iron-driven ROS is the connection it has made to inflammations occurring in the nervous system. This implies that iron-assembled microglia, which are immune cells present in the brain, produce pro-inflammatory cytokines and reactive oxygen species as part of the immune response. As such, chronic inflammation as well as increased iron levels result due to long-term activation of these microglia. This way, oxidative stress is increased by several orders of magnitude. This process results in the quick, progressive increase of neuronal susceptibility as well as the neurodegeneratogenic process itself. Various observations show that the cycle involving the immune response as well as oxidative damage is one of the key elements of the progression of disease. This implies it is not just a byproduct of neuronal death itself. (Chaudhary et al., 2023). This creates a vicious cycle of activated microglia in which iron-induced ROS production fuels neuroinflammation even further, and the resultant neuroinflammation fuels iron accumulation and so on. In this manner, the activated microglia can thus be viewed as the effectors and the initiators of the detrimental process of neuronal cell death/disease progression. This approach of tackling the oxidative burden and metal imbalance has gained traction as an approach in the therapeutic arsenal due to the understanding of its causative rather than purely epiphenomenological role in disease pathogenesis (Charissopoulos et al., 2025). Iron and copper play very significant roles in health and have been observed in disease processes whenever there is an imbalance in concentration with resultant oxidative stress and cell dysfunction, especially in conditions of neurodegenerative diseases such as AD and PD. The complex biological mechanisms implicated in oxidative stress processes suggest an approach aimed at preventing the onset of this detrimental process at an early stage of the disease may be most effective.

Conclusion

In conclusion, oxidative stress can be considered to be the underlying and important link between the onset or development of neurodegenerative diseases of major type, such as PD and AD. In fact, neurons are found to be quite vulnerable to oxidative damage due to their high energy consuming nature, dependence on mitochondria for energy production, lipid rich cell membranes, and low degree of regeneration. Oxidative defense mechanisms normally keep the level of ROS at bay during physiological conditions. However, when the production rate of ROS exceeds the rate at which it can be neutralized by antioxidant defenses, the harmful effects of oxidative stress can be observed. In fact, a number of studies have revealed that oxidative stress can be considered as a factor that actively interplays with neuronal dysfunction and death.

One of the primary reasons why oxidative stress becomes exaggerated in neurodegenerative diseases is due to the disruption of the metabolism of redox active metals, such as iron and copper. Iron and copper ions induce the production of hydroxyl radicals, which, in engaging in Fenton and Haber-Weiss reactions, are able to exert their damaging effects on biomolecules in brain regions that are already severely affected by oxidative stress. Excessive accumulation of these metals not only inactivates antioxidant defense pathways but also promotes lipid peroxidation, protein misfolding, enzyme inactivation, and mitochondrial impairment, all of which result in the disruption of signals and normal function in susceptible neurons. Oxidative damage, once initiated, will continuously propagate itself, as damage to mitochondria will induce the production of ROS, thereby promoting disease progression.

Oxidative stress, apart from direct neuronal damage, is also linked with neuroinflammation through microglia activation. This continuous cycle of oxidative stress, together with microglia, leads to chronicity in the progression of neurodegenerative diseases. Oxidative stress, accompanied by an imbalance in metal ions, largely leads to the process of neuroinflammation, which in turn supports oxidative stress as the main cause of neurodegenerative diseases. Understanding these mechanisms shifts the emphasis from symptomatic treatment to intervention to directly alter the progression of the diseases. This will prevent or reduce cellular damage by limiting oxidative stress, as well as providing a degree of protection from metal-induced toxicity, as well as abnormal protein accumulation. At the same time, overcoming positive inflammatory feedback loops could trigger a decrease in neuroinflammatory processes. Moreover, multifaceted therapeutic approaches may have a cumulative effect in slowing down or even halting the development of pathology if they are initiated in the early stages before the pathology becomes irreversible.

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An Analysis of Upwelling Regions and How They Are Affected by Outside Influences

Kaleb Brunn

Keywords: Upwelling, Climate Change, Human Impacts, Marine Ecosystems

Introduction

Many outside influences affect upwelling regions, which directly impacts the ecosystems around them. These upwelling regions provide benefits for the environment and the marine life around them by transporting the nutrients found at the bottom of the ocean toward the marine life found at the ocean's surface. This action helps provide the marine animals with the nutrients they need to reproduce and flourish. Furthermore, upwelling regions around the world have significant positive and negative impacts on the surrounding marine ecosystems, some of which are driven by other outside influences like human impacts and climate change.

Past sources have explained where different upwelling regions are, how climate change impacts them, and how human impacts affect them. However, few have investigated how human impacts and climate change have greatly affected the marine ecosystems that reside in these upwelling regions. The objective of this paper is to investigate the impacts that human causes and climate change have on upwelling regions.

Specifically, this study proves that climate change, overfishing, and pollution negatively impact upwelling regions, thus limiting their benefits and hurting the surrounding marine environments.

Upwelling Regions: An Overview

There are many different upwelling regions scattered across the surface of our world. Figure 1 shows that in upwelling regions, winds blow across the surface of the ocean pushing some water away from a specific area. When this occurs, water rises from below the surface of the ocean to replace the diverging surface water (National Ocean Service, n.d.). This movement, caused by the winds and different weather changes, helps uproot some of the nutrients at the very bottom of the ocean. This also raises the nutrients high enough that the marine life at the surface of the ocean gets the nutrients and benefits they need to be able to survive (National Ocean Service, n.d.). These upwelling regions are extremely important to the marine ecosystems that reside in or around them. Based on location and outside forces, they may have positive or negative effects on marine life. In this way, upwelling regions have a big impact on marine life []and ecosystems in our world.

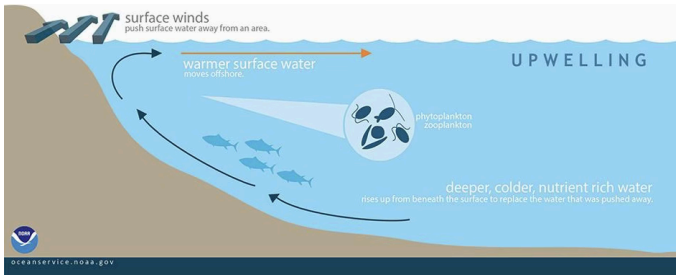

Figure 1: The upwelling process: Colder, nutrient-rich water is brought to the surface while warmer surface water is moved offshore (National Ocean Service, n.d.)

Upwelling regions are located everywhere across our globe. Some of the different upwelling regions are, (i) Peruvian Upwelling, huge upwelling regions where upwelling regularly occurs off the coast of Peru, (ii) Namibian Upwelling, "the coastal waters off southwest Africa where cold, nutrient-rich currents upwell from Antarctica ;and easterly trade winds push surface water away from the shore". This kind of upwelling also allows tiny, little plant-like phytoplankton to thrive and (iii) Four major Eastern Boundary Upwelling Ecosystems located in California, Spain, and western Angola as shown in Figure 2. Figure 2 demonstrates large-scale patterns of spatial and temporal variability (Francisco, 2009).

There are many differences between upwelling regions. These differences consist of physical comparisons like sea level, winds, upwelling, curl, and vertical structure; chemical comparisons like nutrients, oxygen, and carbon dioxide; and biological comparisons like chlorophyll, primary productivity, zooplankton, and small pelagic fish (Francisco, 2009).

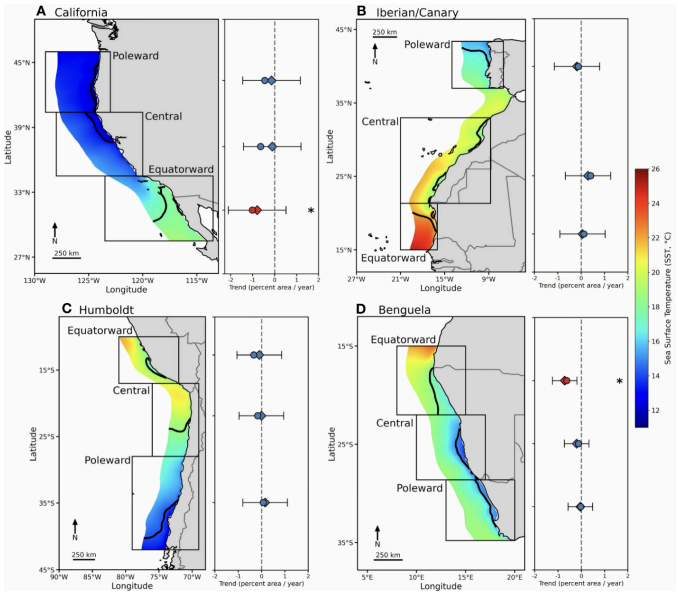

Figure 2: The major Eastern Boundary Upwelling Regions and their sea surface temperatures (Marisol R., 2023)

The Effects of Climate Change on Upwelling Regions

Climate change plays a major role in shaping our world, especially in upwelling regions. The Energy Saving Trust defines climate change as: “the long-term change in average weather patterns and average temperatures across the world.” They expand upon this statement with, “the main cause of climate change is greenhouse gas emissions such as carbon dioxide, which trap in the sun’s heat” (Energy Saving Trust, 2025). By trapping carbon dioxide in the ocean, climate change affects upwelling regions.

One way climate change affects upwelling regions is through changes in the thermocline. The thermoclines of upwelling regions are changed by accumulated heat and mass. These aspects then change the depth and characteristics of the thermoclines. (University of Illinois, 2010). For example, when trade winds accumulate mass and heat in the western side of ocean basins, the thermocline deepens in the west and rises in the east. This benefits marine life by changing ocean temperatures which influences how organisms thrive, reproduce, and gather. However, in certain regions, changes in the thermocline may have undesired effects. (Francisco P.,2009).

Take bays as an example; in bays, wind-driven flow over the shelf imposes circulation in the bay. This circulation has the potential to catalyze coastal upwelling and downwelling, leading to both positive and negative effects on the marine ecosystem. Although coastal upwelling and downwelling has the potential to transport larvae, phytoplankton, nutrients, and sediment between the shore and open ocean, it also has the potential to transfer pollutants. However, the scope of effects are bay-dependent, and vary substantially. In the Grays Harbor bay, California Current Systems occur which are generally considered to be good for marine ecosystems due to the role it plays by providing nutrient-rich upwelling for diverse marine life (National Marine Ecosystem Status, n.d.); while, in the False Bay, the Benguela Current Systems occur, which are both beneficial and harmful to the environment. They are beneficial for bordering countries due to their large fish stocks; however, they also experience struggles such as overfishing and the degradation of the habitats around them (John L., 2020). A final example of climate change affecting marine life is that in coastal upwelling systems, ecosystem productivity is being threatened by this kind of climate change. This is because climate change leads to upwelling intensification which causes ocean acidity to rise. This negatively affects organisms with carbonate structures including corals, oysters, mussels, clams, scallops, and pteropods (National Oceanic and Atmospheric Administration, n.d.) and (A. Baker, 2015).

Human Impacts on Upwelling Regions

Human impacts, defined as impacts caused by the actions of humans (intentional or unintentional), affect upwelling regions. These impacts play a major role in the health of upwelling regions and the marine ecosystems that exist around them. There are many examples of human impacts that affect marine ecosystems in upwelling regions, including, but not limited to, pollutants and fishing.

One way pollution enters upwelling regions is through runoff. Runoff occurs when there is more water than the land can absorb. This water then can run to the sea, potentially picking up pollutants along the way. Runoff commonly dumps litter, petroleum, chemicals, fertilizers, and other toxic and harmful substances into these upwelling regions causing damage to the upwelling regions and their ecosystems. Pollution can be introduced to runoff in many ways including from pipes from sewage treatment plants, factories, or even homes. Trash and plastics can also be introduced into upwelling regions through nonpoint source pollution, which “is any source where runoff does not go directly into a waterway”, and point source pollution, which “ is any source that empties directly into a waterway” (Nation Geographic, n.d.). Some examples of nonpoint source pollution are large urban, suburban, and rural areas; while some point source solutions are pipes, factories, and even homes (Nation Geographic, n.d.).

Furthermore, as the blue economy grows, it lends itself to certain negative effects on upwelling regions. Some of these negative effects result from architectural builders and construction workers developing cities alongside upwelling bay regions as well as marine industry expansion. This development causes dangerous pollutants to discharge into these regions through dumping and harm the marine ecosystem. These pollutants include pathogen pollution, organic pollution, and toxic pollution (John L., 2020), which cause internal damage to organisms and contaminate water, which leads to disease and sicknesses in marine life, disrupting ecosystems. Moreover, overfishing, when too many people are fishing in a particular area, is detrimental to upwelling regions. Overfishing creates a lack of resources for pelagic fish. A lack of resources for the pelagic fish means that there will soon be a lack in pelagic fish production (A. Baker, 2015). This lack in pelagic fish production devastates the marine food chain in these regions, causing more desirable fish, such as fish used for human consumption, not be able to reproduce.

Conclusion

In conclusion, climate change, overfishing, and pollutants are harming the ecosystems around upwelling regions. For example, the location of certain upwelling regions has major impacts on the effects of the marine ecosystems in those areas. If an upwelling region is located where trash and pollutants are prominent, then that upwelling region will be more at risk. Furthermore, another example is climate change. Climate change has consequences for many environments, including upwelling regions and their ecosystems. Finally, human impacts including fishing, pollutants, and runoff play significant roles in the health of upwelling regions and their surrounding ecosystems. There is a need for society to be mindful of the upwelling regions in our environment. Not doing so leads to devastating problems such as a lack of resources for pelagic fish which leads to a lack of desired consumer fish. This carelessness also affects the industries in surrounding cities by providing them with a lack of resources. However, there are still many ways that the world and environment can care for marine ecosystems across the globe. For example, if unaffected by outside influences, upwelling regions are able to benefit marine life by transferring nutrients from the bottom of the ocean to the surface. This helps to provide all necessary nutrients the marine animals need in order to reproduce and flourish throughout their lifetime. For these reasons, it is necessary to put limits on fishing and cease dumping trash in upwelling regions.

There are some limitations in my study to consider. Some of the sources I used are not up to date. Some of the sources I have used date back to 1970. Another limitation of my study is that the topic of upwelling needs frequent samples and studies because the ocean is constantly changing. Additionally, there have not been comprehensive studies of all important upwelling locations. Further study of these regions is imperative.

A strong implication resulting from this study is that society needs to stop polluting the oceans and being reckless around upwelling regions. This is because reckless human behavior can cause a lack of resources for fish and marine ecosystems which could be harmful or cause a lack in their reproduction. This endangerment of the marine ecosystem also harms us because it takes away some of the resources that adjacent communities rely on.

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