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A Review of the Role of Keratinocytes in Psoriasis

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Abstract

Psoriasis is primarily initiated by metabolic, signaling, and gene regulatory alterations within keratinocytes, which often arise before the immune system becomes fully activated (Zhou et al, 2022). Keratinocytes are not simply passive targets of inflammation; instead, they actively produce inflammatory mediators that accelerate their own proliferation and disrupt epidermal homeostasis (Ni & Lai, 2020). These early molecular disturbances reposition keratinocytes as primary initiators of disease. As these disruptions accumulate, the keratinocyte cell cycle shortens dramatically, from approximately twenty-eight days to just a few days, resulting in rapid epidermal thickening and formation of characteristic psoriatic plaques.

Multiple studies have identified specific pathways that drive this abnormal growth. One example is the overactivity of LPCAT1, a lipid metabolism enzyme whose elevation in psoriatic keratinocytes activates STAT3 and NF-κB signaling, two major regulators of proliferation, survival, and inflammatory gene expression (Huang et al., 2024). LPCAT1 also increases glucose uptake through GLUT3, supplying metabolic fuel for hyperproliferative keratinocytes (Huang et al., 2024). These findings illustrate how metabolic changes directly promote both excessive growth and inflammation.

Zhou et al. (2022) further show that transcription factors and noncoding RNAs reshape gene expression programs in psoriatic keratinocytes. These regulatory changes amplify expression of genes involved in proliferation while suppressing differentiation pathways, disrupting normal epidermal maturation and accelerating plaque development. Their results indicate that keratinocytes undergo coordinated transcriptional reprogramming that enables them to maintain a highly proliferative and inflammatory state. Collectively, these studies demonstrate that psoriasis originates from keratinocyte-driven molecular disturbances that precede and initiate immune activation. Altered metabolism, dysregulated signaling pathways, and disrupted gene regulatory networks together push keratinocytes into continuous overgrowth while creating a pro-inflammatory environment that sustains disease progression.

Cytokines as Drivers of Psoriasis

Cytokine signaling is another central driver of keratinocyte hyperproliferation in psoriasis and results from genetic susceptibility and immune dysregulation. Cytokines are small signaling proteins secreted by immune and non-immune cells that regulate inflammation, cell growth, and tissue homeostasis, playing a key role in coordinating the immune response in psoriasis (Griffiths et al., 2021). Variants affecting immune regulatory pathways can heighten cytokine production and shift keratinocyte behavior from controlled growth to sustained activation (Griffiths et al., 2021). Central to this inflammatory response is the TNF-α / IL-23 / IL-17 axis. Cytokines within this network activate keratinocyte receptors and trigger intracellular signaling cascades such as STAT3 and NF-κB, which in psoriasis remain chronically active (Griffiths et al., 2021; Huang et al., 2024).

Persistent activation promotes keratinocyte proliferation, induces chemokine release, and recruits additional immune cells, reinforcing the inflammatory cycle.

Further evidence shows that IL-17 cytokines directly stimulate keratinocytes to produce antimicrobial peptides, chemokines, and inflammatory mediators (Lowes et al., 2014). IL-23 sustains pathogenic Th17 cells, which secrete IL-17A, IL-17F, and IL-22—cytokines that accelerate keratinocyte proliferation and impair normal differentiation (Hawkes et al., 2023). Zhou et al. (2022) also demonstrate that keratinocytes themselves produce cytokines such as IL-17C, IL-23, and IL-36, generating autocrine inflammatory loops that independently amplify their activation.

Genetic loss of IL36RN, which encodes the IL-36 receptor antagonist, removes an essential brake on IL-36 signaling. This leads to excessive cytokine and chemokine production, heightened neutrophil recruitment, and severe keratinocyte hyperproliferation—mechanisms linked to generalized pustular psoriasis (Frontiers in Immunology 2023; Bachelez 2022). These findings affirm that cytokine dysregulation operates at multiple levels and that keratinocytes actively contribute to sustaining chronic inflammation.

Clinical Treatments to Psoriasis

Therapeutic strategies for psoriasis focus on interrupting the molecular and immune-driven mechanisms that cause keratinocyte hyperproliferation. One key target is metabolic regulation within keratinocytes. FBP1, a critical enzyme in gluconeogenesis, controls keratinocyte proliferation and differentiation by regulating histone acetylation, which affects gene expression programs associated with growth and maturation (Zhang et al., 2024). In psoriatic skin, reduced FBP1 expression shifts keratinocyte metabolism toward glycolysis, providing energy that supports rapid proliferation, while increasing histone acetylation to promote pro-growth gene expression (Zhang et al., 2024). Experimental deletion of FBP1 in mouse models further intensified psoriasiform inflammation, highlighting its therapeutic potential as a molecular target for restoring normal epidermal growth (Zhang et al., 2024).

Natural compounds have also demonstrated potential in regulating both keratinocyte proliferation and inflammation. Apigenin, a plant-derived flavonoid, significantly reduced plaque severity, epidermal thickness, and inflammatory markers in psoriatic mouse models (Alimujiang et al., 2025). Functionally, Apigenin inhibits the CDK2/E2F2 cell cycle pathway, which controls keratinocyte proliferation and suppresses IL-17–mediated cytokine signaling, demonstrating dual efficacy in targeting keratinocyte-intrinsic growth and immune-mediated inflammation (Alimujiang et al., 2025).

Biologic therapies represent a major advancement in psoriatic treatment by targeting specific cytokines that drive disease. Unlike traditional systemic agents, biologics selectively block TNF-α, IL-17, or IL-23, disrupting the cytokine receptor–mediated signaling essential for keratinocyte activation (Griffiths et al., 2021). This includes anti-TNF agents that neutralize TNF-α, anti-IL-17 biologics that block IL-17A activity, and anti-IL-23 therapies that prevent IL-23–driven expansion of IL-17–producing T cells (Griffiths et al., 2021). Clinical trials demonstrate that these treatments achieve higher clearance rates, longer remission, and fewer systemic side effects than older therapies (Griffiths et al., 2021).

Evidence suggests that combining metabolic interventions with cytokine-targeting biologics may yield synergistic benefits (Zhang et al., 2024; Alimujiang et al., 2025). Restoring

FBP1 activity or mimicking its effects could complement biologics by addressing both keratinocyte-intrinsic and immune-mediated drivers of disease.

Conclusion

Recent findings have redefined the understanding of psoriasis by demonstrating that keratinocyte metabolism, signaling, and cytokine interactions lie at the core of disease development. Reduced expression of FBP1 promotes glycolytic metabolism and increased histone acetylation, driving keratinocyte overgrowth, while experimental deletion of FBP1 markedly intensifies inflammation in mouse models (Zhang et al., 2024). Natural compounds such as Apigenin further support therapeutic innovation by suppressing keratinocyte proliferation and IL-17 signaling (Alimujiang et al., 2025). Clinical evidence shows that biologic therapies targeting TNF-α, IL-17, and IL-23 achieve superior outcomes compared to traditional systemic treatments (Griffiths et al., 2021). Collectively, research supports a shift toward precision therapies that treat both the metabolic and immunologic mechanisms sustaining psoriasis. Continued investigation into metabolic pathways, natural therapeutics, and advanced biologics may lead to more durable and personalized treatments (Zhang et al., 2024; Alimujiang et al., 2025; Griffiths et al., 2021).

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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), 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^{6}A 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^{6}A Modification of MALAT1

Recent studies have provided direct evidence that m^{6}A 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^{6}A 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^{6}A 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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fMRI-Based Deception Detection and Forensic Validity

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March 2026

Abstract

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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The Influence of Resistance Training Volume, Intensity, and Frequency on Muscle Hypertrophy

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Abstract

Previous studies have demonstrated a linear relationship between muscle hypertrophy and exercise volume; however, increases in exercise volume beyond a certain threshold may result in a plateau in which increasing exercise volume may have limited effects on increasing muscle hypertrophy (Baz-Valle et al., 2022; Bernárdez-Vázquez et al., 2022). A systematic review conducted by Baz-Valle et al. (2022) examined moderate and high exercise volumes, defined as 12-20 sets per week and over 20 sets per week, respectively. No significant differences were shown between the two volume levels for hypertrophy for the quadriceps and biceps muscles between the two exercise volumes; however, a minor increase in hypertrophy for the triceps was demonstrated at the higher volume level. Thus, increasing exercise volume past 20 sets per week is unlikely to result in greater hypertrophy than a moderate exercise volume, suggesting that a volume of 12-20 sets per week is sufficient. These findings are further supported by an umbrella review conducted by Bernárdez-Vázquez et al. (2022), demonstrating that an exercise volume of 10 sets per week is required for notable increases in muscle hypertrophy; however, high exercise volumes of over 20 sets did not result in significant increases in hypertrophy.

These findings demonstrate that exercise volume is influential to muscle hypertrophy; however, muscle hypertrophy is not solely dependent on exercise volume. Additional factors, such as exercise frequency, examined by Schoenfeld et al. (2016), while not directly influential to muscle hypertrophy, interact with exercise volume as a method to manage fatigue. Schoenfeld et al. (2016) demonstrated that an exercise regimen focused on training twice per week resulted in greater hypertrophy over training once per week. However, when controlling for exercise volume, increases in hypertrophy were not affected by increased exercise frequency. This suggests that exercise volume is the primary factor affecting muscle hypertrophy, but that increased exercise frequency of multiple sessions, such as two or three sessions per week, may help manage muscle fatigue.

Intensity of Exercise

Training intensity, traditionally defined as load relative to an individual's one repetition maximum (RM), but more accurately conceptualized as proximity to muscular failure, has been previously viewed as an essential factor in increasing muscle hypertrophy (Carvalho et al., 2022). The proposed mechanism has been described as heavier loads induce greater mechanical tension to drive hypertrophy. However, recently it has been demonstrated that exercise intensity over a wider range of repetitions, so long as the total exercise approaches muscle failure, may result in similar benefits (Lopez et al., 2021).

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Figure 1. Forest plot comparing resistance-training loads and hypertrophy outcomes (Lopez et al., 2021). The points represent the standardized mean difference for each study. These comparisons demonstrate no significant difference between loads, indicating that increases in muscle hypertrophy are not influenced by specific loading when total effort is matched.

Previous studies compared low load (≥15RM), moderate load (9-15RM), and high load (≤8RM) training across 28 studies, and found non-significant differences in hypertrophy between training loads (Figure 1), demonstrating that muscle hypertrophy may be load independent. This favors training regimens that approach muscle failure at the end of the exercise, rather than any specific weight or repetition count. However, high load significantly increases strength gain (Figure 2). Strength gain is the improvement of one's ability to produce force, usually measured through an increase in weight or repetitions.

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Figure 2. Forest plot (Lopez et al., 2021) illustrating the effects of low, moderate, and high training loads on muscle strength across multiple studies (Lopez et al., 2021). Higher loads are consistently shown to favor greater strength gains compared to lower loads, with significant differences between loads.

Another meta-analysis (Carvalho et al., 2022) tested this idea by matching volume (equation 1) across very-low (<30%1RM), low (30–59%), moderate (60–79%), and high (≥80%) intensities. When overall work was equal, the authors reported that there was no significant difference across any load for hypertrophy. Once again, strength shows a clear load dependence, increasing when the load is high.

These two studies together demonstrate that hypertrophy is load-independent within the 20-85%1RM range, as long as the training is performed close to failure. Research shows lower loads can stimulate growth, but they need more repetitions and may generate more fatigue to reach failure. Higher loads, however, are more efficient and maximize strength gain, making them the most practical option for most individuals. Overall, these studies show that intensity should be viewed as the proximity to failure used, rather than the specific load used.

Frequency of Exercise

Training frequency, defined as the number of times a muscle is trained per week, is another variable of interest in addition to volume and intensity. Recent work suggests that the distribution of weekly volume across sessions is more effective than concentrating all of the weekly volume into one session (Schoenfeld et al. 2016). Shoenfeld compared training a muscle once per week vs. two or more times per week and demonstrated that higher frequencies resulted in a greater increase of muscle hypertrophy overall, even when total sets were not matched. In these studies, higher frequency groups performed more overall weekly sets, potentially explaining the increase in hypertrophy. Training the muscle multiple times per week can be an effective way to increase muscle hypertrophy by allowing for more volume and enhanced recovery between sessions.

A later meta-analysis in 2019 (Schoenfeld et al., 2019) equated weekly volume across all groups to determine how frequency independently affects growth. When individuals performed the same total number of sets over a week, independent of a specific training schedule, Schoenfeld demonstrated that resistance training frequency is not directly influential to muscle hypertrophy when volume is equated (Schoenfeld et al., 2016; Schoenfeld et al., 2019).

Together, these demonstrate that frequency is helpful mainly through indirectly allowing weekly volume to be distributed to enable higher quality recovery, higher quality sets, and better proximity to failure. By performing weekly sets across a week, one can prevent fatigue from accumulating, thus allowing each session to be of the same quality.

Conclusion

In summary, previous studies have demonstrated that hypertrophy is influenced by exercise volume, intensity, and frequency. However, these variables are not equally influential. Training volume remains the most outsized factor that drives increases in muscle hypertrophy, with 12-20 weekly sets per major muscle group resulting in optimal hypertrophy (Baz-Valle et al., 2022; Bernárdez-Vázquez et al., 2022). However, additional volume beyond this range does not reliably increase hypertrophy and may contribute to building unnecessary muscle fatigue. Previously, exercise intensity was hypothesized as the driving variable due to its relationship with mechanical tension; however, it has been shown that it is effective across a wide range of loads, as long as they are performed close to failure (Lopez et al., 2021). Low, moderate, and heavy loads all increase hypertrophy, with no significant differences between specific loading. However, heavy loads have a positive and significant relationship with increases in overall strength, while lower loads may increase fatigue due to a greater number of repetitions in a session. Thus, it is important to redefine intensity as proximity to failure, not the weight of a movement.

Frequency, while stressed in recent bodybuilding programs, has been shown to potentially have an indirect impact on hypertrophy, rather than a direct one. When volume is matched, exercise frequency of one, two, or three sessions per week yields equivalent increases in hypertrophy (Schoenfeld et al., 2016; 2019). However, higher frequencies enable the individual to effectively distribute weekly volume, thus minimizing fatigue and maintaining higher quality sessions throughout the week. Therefore, frequency should be seen as a tool to handle volume and fatigue, rather than a direct variable for hypertrophy.

When taken together, these studies show that the most effective strategy for maximizing muscle hypertrophy is a training regimen that prioritizes sufficient weekly volume, high effort sets that are taken close to failure, and employs a higher frequency to maximize performance quality and recovery. As no single variable operates independently, understanding how these variables complement each other, athletes, bodybuilders, and individuals who are interested in improving their overall physical well-being can design a program that is evidence-based and efficient for muscle hypertrophy (Baz-Valle et al., 2022; Lopez et al., 2021).

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Multimodal Music Emotion Recognition: Benchmarking LLM, Audio, and CNN Approaches

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Abstract

The core research topic at the heart of this project is the accuracy with which an AI/ML model can classify emotions in music through audio and lyrics and how they can use features like arousal and valence to do so. Music Emotion Recognition (MER) remains challenging because audio and lyric messages capture different aspects of emotion. We created a multimodal benchmarking system that evaluates (1) a zero-shot 7B LLM (OpenChat 3.5) on lyrics (a model with 7 billion parameters that's given a task without any specific training examples in the prompt, with clear instructions), (2) an audio Random Forest using MIR features (a common machine learning approach for audio analysis and classification tasks), and (3) a CNN spectrogram model (uses Convolutional Neural Networks (CNNs) to analyze audio by first converting sound into visual spectrogram images (time-frequency representations), then feeding these "images" into the CNN to find patterns for tasks like emotion recognition) Dylan7e [2025] for continuous valence–arousal (VA) regression (approach in affective computing that uses machine learning to predict emotional states as continuous numerical values for valence (positivity/negativity) and arousal (intensity)). The LLM achieves 50.7 percent accuracy on eight-class emotion labels, outperforming the audio Random Forest (≈ 40 percent accuracy on VA-mapped labels). The CNN baseline attains normalized RMSEs of 0.1678 (valence) and 0.1972 (arousal). Calibration analysis shows the CNN is well-calibrated (ECE 0.0143), while the LLM is less aligned but provides interpretable rationales. Compared with prior single-modality MER systems, our framework highlights complementary strengths—audio better captures arousal, lyrics improve valence—and shows that integrating LLM classification yields more interpretable and reliable emotion predictions.

1. Literature Review 1.1. Technical Theoretical Models In the paper Gökalp [2019], Cembre Gokalp conducted a 2019 study to develop predictive models of musical emotions through audio and textual analysis in his research. The research evaluated the performance of audio-only models against models that used lyrics through supervised and semi-supervised learning methods. The research findings indicated that audio-only models achieved 44 percent accuracy yet models that included lyrics reached 46 percent accuracy with supervised learning and 51 percent accuracy with semi-supervised learning. The study supports our research inquiry because it shows how Music Emotion Recognition (MER) reveals the connection between musical elements and emotional responses. The paper offers essential knowledge about how audio features compare to lyrics in MER systems and demonstrates that using multiple learning paradigms produces better results

than using a single approach. Another study, Juthi et al. [2019], analyzed how music emotion recognition systems detect the emotional connections between musical elements and listener responses. The researchers extracted eight audio features from music including pitch and tempo and timbre and brightness to create four mood categories according to Russell's emotion model and psychological theories. The researchers tested different classification methods including support vector machines and ensemble methods and artificial neural networks to evaluate system performance. The neural network achieved the highest prediction accuracy of 75 percent through the combination of all eight features. The researchers demonstrated that the audio feature recognition process operated at high speed by taking only 0.004 minutes to produce results which matched human emotional perceptions of music. The research aligns with our investigation because it employs MER and feature extraction to analyze musical emotional effects yet employs Matlab's MIR Toolbox and focuses on multiple classification method evaluation. More recently, in Lian [2023], researchers at a Malaysian University created an AI system which identifies musical emotions through applications for media education. The research team focused on audio feature extraction instead of using pre-marked content such as lyrics in their approach. The researchers applied sound segmentation techniques to process data frames while establishing threshold values for precise note detection. The Radial Basis Function (RBF) model served as the classifier's foundation while correlation feedback enabled the training process to become more precise. The system divided emotions into four categories which included quiet, happy, sad, and excited, and it performed better than conventional classification techniques. The system reached a remarkable accuracy level exceeding 95 percent while it processed audio in less than 0.004 minutes. The system operates at a speed that matches human emotional responses to music.

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1.2. Nontechnical Theory More recently, in Lian [2023], researchers in Malaysia created an AI system which identifies musical emotions through applications for media education. The research team focused on audio feature extraction instead of using pre-marked content such as lyrics in their approach. The researchers applied sound segmentation techniques to process data frames while establishing threshold values for precise note detection. The Radial Basis Function (RBF) model served as the classifier's foundation while correlation feedback enabled the training process to become more precise. The system divided emotions into four categories which included Quiet and Happy and Sad and Excited and it performed better than conventional classification techniques. The system reached a remarkable accuracy level exceeding 95 percent while it processed audio in less than 0.004 minutes. The system operates at a speed that matches human emotional responses to music. Swaminathan and Schellenberg [2015] analyzed studies from 2000 onwards to understand how music communicates and generates emotional responses in different cultural settings. The researchers combined psychological studies which studied how people perceive and experience and choose musical emotions. The researchers determined that music expresses emotions through two types of elements which include universal acoustic signals and specific cultural musical characteristics that include Western major and minor modes. The research shows

that music listeners understand emotional content in music through their perception and also experience emotional responses when listening to music according to the available evidence. The research provides essential knowledge about musical features that trigger emotional recognition but it focuses on human psychological processes instead of machine learning accuracy. In the paper Scherer [2004] from University of Geneva researched which emotions music can create, their origin, and their measurement methods. The author analyzed three emotion measurement theories which include basic emotions and valence-arousal dimensions and eclectic inventories to evaluate their effectiveness in detecting music-evoked emotional responses. According to him music creates emotions that differ from survival-based utilitarian feelings because it generates specific aesthetic emotions which include awe and wonder and transcendence. According to his analysis classical music pieces fail to generate intense basic emotions that include anger fear disgust and desperation. The research establishes the challenges of emotional labeling in music which affects AI/ML emotion datasets, yet employs psychological approaches instead of model precision assessment. In the paper Yoo et al. [2024] from Korean universities researched music emotion recognition through multi-class classification. The researchers investigated two main aspects of their study which involved automatic emotion classification of multimedia background music and the identification of optimal machine learning approaches for accessibility applications. The researchers used a Kaggle dataset containing 2,500 audio clips which received five emotional labels (Aggressive, Dramatic, Happy, Romantic and Sad) to extract MFCC, RMS and Mel Spectrogram features before testing four machine learning models including

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Logistic Regression, Support Vector Classification, AdaBoost, and Random Forest. The Random Forest classifier produced the best results by achieving 94.8 percent accuracy in the experiment. The researchers support their findings through experimental results which demonstrate the practical value of this technology by showing Random Forest achieves the best accuracy rates. The study matches our research by assessing model precision for emotion detection but it uses audio features, receiving exclusive analysis for OTT service accessibility needs instead of combining audio and lyrics for AI performance evaluation. Lian [2023] also includes non-technical theoretical aspects through its assumptions about human emotional response classification to music. The researchers used four emotional categories which included Quiet and Happy and Sad and Excited to represent a basic psychological model of emotional responses. The researchers based their emotional grouping on broad affective states because they designed the system to match human emotional processing speed. The paper connects computational theory with human-centered emotion theory through its design approach which incorporates psychological assumptions and real-world media education experiences.

1.3. Software Packages Used Dylan7e [2025] uses the dataset Gupta [2021], for emotion analysis in music, to build a model for music emotion recognition with CNN. It prepares the data, then converts raw audio to mel-spectrograms with the

librosa library. Mel-spectrograms map them onto the mel scale. Then, the data is split at the song level. Data normalization occurs, and the model is trained. The MSE (mean squared error) and RMSE (root mean squared error) are caclculated. We drew most of our code for this project from Chandrasena M.M.D. [2023]. The model design combines traditional feature engineering techniques with deep learning methods to enhance audio signal emotion classification accuracy. The flowchart in Fig. 1 shows how the system uses openSMILE to extract handcrafted acoustic features from raw audio signals. The standardized feature set undergoes selection to determine which variables produce the best results for emotion prediction. The BLSTM network receives the chosen features to detect temporal patterns in audio data. The BLSTM network produces dynamic AV values which the DNN transforms through nonlinear operations before the model applies Thayer's two-dimensional emotion model for emotion classification. The second processing stream uses a Convolutional Neural Network (CNN) to analyze audio data directly without requiring manual feature extraction. The CNN system discovers emotional content patterns through automatic waveform analysis to generate spatial and temporal representations. The model combines CNN-generated features with openSMILE-derived handcrafted features to achieve better results through the combination of learned data patterns and domain-specific acoustic descriptors. The system maintains both low-level temporal information and high-level semantic patterns through multimodal fusion before the shared feature selection and classification stages which results in better 3

Figure 1: Methodology Architecture Model from Chandrasena M.M.D. [2023] emotion recognition accuracy. Definition 1.1 (Valence). The positive or negative quality of an emotion Definition 1.2 (Arousal). The intensity or energy level of an emotion Fig. 3 and Fig. 2 show that the arousal and valence models (see Definition 1.1 and Definition 1.2 for definitions). have identical structures but they produce different output results. The network starts with 159 input features which include both manually created attributes and attributes extracted by CNN from audio data. The input data passes through a Bidirectional CuDNNLSTM layer containing 64 units which analyzes temporal relationships across both forward and backward time directions. The network uses bidirectional processing to detect audio signal changes which affect emotional intensity and positivity perception. The Flatten layer transforms temporal output into a format which allows the network to use it in following dense layers. The network processes the flattened data through dense layers which decrease in size from 512 to 256 to 128 to 64 to 32 neurons while using ReLU activation to introduce nonlinearity and extract hierarchical features. The network uses dimensionality reduction to transform complex emotional information into simpler yet more effective representations. The network produces binary output through a single-unit dense layer with ReLU activation which classifies audio into high/low arousal or positive/negative emotional states. The system merges recurrent temporal processing with deep feedforward networks to detect emotional states with high precision in both arousal and valence dimensions.

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Figure 2: Arousal Architecture Model from Chandrasena M.M.D. [2023]

2. The Model 2.1. Data Availability For our model, we used the Music4All dataset, a large, multi-modal collection for Music Information Retrieval (MIR) research, featuring over 100,000 songs with rich data: metadata (artist, album, year), audio clips, lyrics, genres, user-generated tags, and acoustic features (danceability, energy, tempo, etc.). It's designed to support diverse MIR tasks by providing data across different "layers" from raw audio to subjective user content.

2.2. Our Model In Fig. 6, the emotion classes "Sadness", "Love", and "Joy" have a strong performance differing from emotions like "Anger" and "Calm". This matrix showcase sparse uncertainty in low-frequency classes such as "Surprise" or "Unknown" highlighting emotional ambiguity in lyrical phrasing and limitations in LLM confidence calibration. In Fig. 8, the emotion classes "sadness" and "love" have a strong performance whereas emotions such as "anger" and "calm" were misclassified the majority of the time. The diagonal dominance shown is only limited to the high-frequency emotion classes, highlighting bias introduced by class imbalance.

2.3. Comparisons with Our Model Instead of using raw frequencies, mel-spectrograms map them onto the mel scale. Feelings in music show up in patterns of sound, like speed and tone. For example: Fast and lively sounds (high arousal/valence) often feel energetic and happy. Slow and deep sounds 5

Figure 3: Valence Architecture Model from Chandrasena M.M.D. [2023]

Figure 4: Model Loss and Model MAE from Dylan7e [2025]

Figure 5: Valence and Arousal: Actual vs Predicted from Dylan7e [2025]

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Figure 6: Confusion matrix for classification of lyrics against the OpenChat LLM predictions(0 = "Anger," 1 = "Calm," 2 = "Fear," 3 = "Joy," 4 = "Love," 5 = "Sadness," 6 = "Surprise," 7 = "Unknown"). From Vivian Cai

Figure 7: Confusion matrix for classification of lyrics against the ground truth labels from the metadata arousal and valence scores (0 = "Anger," 1 = "Calm," 2 = "Fear," 3 = "Joy," 4 = "Love," 5 = "Sadness," 6 = "Surprise," 7 = "Unknown"). From Vivian Cai In Fig. 7, the emotion class "Love" has strong classification patterns whereas other classes show misclassification. (low arousal/valence) feel calm or sad. The mel-spectrograms in Fig. 9 do a great job of capturing these patterns. The valence-arousal plane for song ID 10 in Fig. 10 shows the mean valence score (1-9) to be 4 and the mean arousal score from (1-9) to be roughly between 4 and 5. This shows a moderate score for both measures. Fig. 11 shows that the average absolute error per segment is about 0.4 units on the 1-9 scale, which is quite low and indicates good segment-level accuracy for song id=47. This is well below the overall test RMSE (0.1664 for valence, 0.1957 for arousal), suggesting song id=47 is easier to predict than the average test song. Fig. 5 shows that the model overpredicts both valence and arousal by about 0.3-0.4 units on the original scale. This consistent bias suggests the model might be slightly skewed toward higher values, possibly due to the training data distribution or feature representation. The field of music emotion recognition (MER) includes both

basic feature-based classifiers and advanced multimodal and language-based systems that operate at different levels of computational complexity. The evaluation of models at various complexity levels shows how their accuracy and interpretability and emotional sensitivity depend on their computational power and input variety and learning approach. The multimodal LLM-driven system developed in this project combines audio features with lyric semantics and valence–arousal 7

Figure 8: Fig 3. Confusion matrix for the audio pipeline to compare the predicted emotion labels against the true emotion labels. From Vivian Cai

Figure 9: Mel-Spectrogram for Song ID 10 (full and first 5s Segment) from Dylan7e [2025] metadata to create its complex model. The supervised deep-learning architecture of Chandrasena M.M.D. [2023] uses learned acoustic representations as its primary input. The low-complexity model of Dylan7e [2025] uses basic feature extraction methods with basic statistical classification algorithms. The three systems demonstrate the progressive development of MER research through their different methodological approaches. We developed a multimodal benchmarking system that places an LLM-centered lyrical pipeline alongside an audio pipeline and valence–arousal metadata to study AI music emotion recognition. Specifically, we used OpenChat 3.5 as a zero-shot lyric classifier: for each song the model produced (a) one of eight discrete emotion labels (joy, sadness, fear, anger, love, calm, surprise, unknown), (b) a numeric confidence score representing its confidence from 1-100, and (c) a brief rationale for the choice. To classify emotions with audio, we extracted standard MIR features (13 MFCCs, spectral centroid, RMS energy, tempo, etc.) from the Music4All songs and trained a Random Forest audio classifier (200 trees) (an ensemble machine learning algorithm primarily used for classification tasks, operating by constructing a ”forest” of multiple decision trees during training and then outputting the class that is the mode of the classes predicted by individual trees. In this case, a random forest classifier is used by first extracting audio features from the songs, then using a training dataset to build an ensemble of decision trees that vote on the final emotion. The algorithm’s effectiveness comes from combining multiple trees to improve accuracy and reduce overfitting, leading to reliable predictions of emotions like happy, sad, or angry.) to predict the same VA→label mapping. Valence–arousal metadata from Music4All was mapped into 8

Figure 10: Valence-Arousal Plane for Song ID 10 from Dylan7e [2025]

Figure 11: Model Loss and Model MAE from Dylan7e [2025] the eight emotion categories using a Russell-circumplex function and used as our primary evaluation reference. Our LLM contribution is twofold: first, demonstrating that a large language model applied to lyrics can reach substantive classification performance (50.7 percent accuracy; macro F1 0.257) on an eight-class MER task without fine-tuning; second, showing that the LLM’s self-reported confidences and rationales are actionable signals for interpretability and for calibration analysis (we assessed confidence–accuracy relationships, MSE of confidence predictions, and ECE-style diagnostics). Together these elements enable explicit cross-modal comparison: we

not only measure what each modality predicts, but also when and why they disagree, and how reliably each model reports its own uncertainty.

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2.4. Key Concepts 2.4.1

7 Billion Parameter LLMs

A 7B parameter LLM is a large language model with approximately 7 billion trainable parameters, which are the values it learns during training to perform tasks like text generation and pattern recognition. These models, such as Mistral 7B, are known for their efficiency and are often smaller, faster, and less resource-intensive than larger models, making them suitable for applications with constrained resources. Key architectural innovations like grouped-query attention (GQA) and sliding window attention (SWA) improve inference speed and the ability to handle longer sequences. OpenChat 3.5 is a 7 billion (7B) parameter large language model (LLM). It is an open-source model designed for conversational tasks and has been benchmarked as a competitive model, sometimes outperforming other popular LLMs. It uses 7 billion parameters to provide a balance of capability and efficiency. 2.4.2

Zero-shot prompting

Zero-shot prompting is an AI technique where a model performs a task using only a natural language instruction, without being given any examples of the desired output. It relies on the model's pre-trained knowledge to understand the request and generate a response, making it great for many applications like sentiment analysis. 2.4.3

Cross-modal benchmarking

Cross-modal benchmarking for LLMs means testing how well models understand and connect information from different types of data (text, images, audio) by evaluating their ability to handle tasks that mix these formats, like describing an image in words or answering questions about a video, assessing consistency, reasoning, and spotting contradictions across these modalities, rather than just within one. In this case, the two different types of data are text and audio features. 2.4.4

Supervised/unsupervised training

LLMs use both unsupervised and supervised training: Unsupervised pre-training on massive text data teaches them language fundamentals (grammar, facts) by predicting the next word (self-supervised), finding patterns without labels. Then, Supervised Fine-Tuning (SFT) uses smaller, labeled datasets (e.g., instruction-response pairs) to align the model's behavior, making it helpful, safe, and follow instructions, essentially teaching it how to answer usefully.

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2.5. High Complexity This section covers the high complexity case, as treated in our LLM model, Vivian Cai What it does: uses a 7B-parameter style LLM (OpenChat

3.5) in zero-shot prompting to convert lyric text into emotion labels, confidences, and rationales; runs a conventional audio pipeline for cross-modal benchmarking; evaluates both against emotions mapped from valence and arousal labels from Music4All dataset. Performance and behavior: lyric LLM = 50.7 percent accuracy and macro F1 = 0.257 when evaluated against lyric-derived labels; audio Random Forest: 40 percent accuracy against VA-mapped labels. The LLM excels at lyric classification and thus performs relatively well on lyric-driven emotions (e.g., love, sadness). It struggled with rare classes (fear, surprise) and with cases where genre, audio or cultural context matters. Calibration analysis showed that audio probabilities were tightly calibrated (ECE ≈ 0.0143), while the LLM's confidence signals were moderately informative but less well aligned with accuracy. Strengths: semantic classification and interpretation, interpretability via rationales, ability to generate confidence estimates without supervised retraining. Weaknesses: zero-shot LLMs are sensitive to lyrics wording, can be overconfident in ambiguous cases, and do not take in the acoustics (tempo, energy) directly; mapping continuous valence/arousal values to discrete emotion labels creates label noise that can hinder measured accuracy. This model shows that lyrics-driven classification models can classify well where lyrics carry the emotional signal, and that LLM confidence + rationales provide a practical route to trustworthy, interpretable MER — but acoustic cues are essential for many songs, so multimodality is required for higher real-world accuracy.

2.6. Medium Complexity This section covers the medium complexity case, as treated in Chandrasena M.M.D. [2023]. This is an engineered deep-learning pipeline focused on audio: openSMILE/handcrafted acoustic feature extraction combined with learned CNN/CuDNN-BLSTM (and BiLSTM + DNN) architectures to predict valence/arousal continuously (dynamic MER) and to classify via VA→discrete mappings. The work also explores DBLSTM, multi-scale context attention, PCA/CFS feature selection, and regression-based approaches (SVR, piecewise regression) for VA prediction. These models typically outperform simple feature-based classifiers for dynamic VA prediction because they use temporal context (past and future frames) and multi-scale attention; they show stronger recall on low-arousal emotions and reliable arousal detection because acoustics correlate well with arousal. Like our audio baseline, they face persistent trouble recovering valence because valence a lot of times is grounded in lyrics meaning and often requires context beyond short acoustic snippets. Chandrasena M.M.D. [2023] reports gains from hybrid fusion (CNN-derived learned features + handcrafted descriptors) and from PCA for feature reduction.

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This project has superior temporal modeling (sequence regression to VA), data efficiency relative to large LLMs and better control over training and calibration when supervised labels are available. However, it has limited access to lyrical meanings (unless lyric embeddings are added), sensitivity to labeling noise in VA mappings, and domain-adaptation challenges across genres and cultural contexts. Medium models provide the most straightforward route to accurate arousal prediction and to time-resolved emotions; they are the preferred approach when

continuous VA estimation and resource constraints are priorities, but they should be combined with semantics (lyrics) to improve valence recovery.

Figure 12: Dimensionality reduction in PCA

2.7. Low Complexity This section treats the low complexity model case. We follow Dylan7e [2025]. What it does: CNN trained on 5-second mel-spectrogram segments (128 mel bins, n fft=2048, hop length=512) from the DEAM dataset (song-level splitting to avoid leakage). Labels are continuous valence and arousal (1–9), normalized for training; the CNN regresses to the two VA values and performance is measured via MAE/MSE/RMSE after inverse scaling. The model uses straightforward data normalization and early-stopping and reports segment-level errors as well as song-level means. Normalized test RMSEs: valence 0.1678, arousal = 0.1972 (1.33 and 1.57 on the original 1–9 scale after scaling), with mean segment MAE 0.05 (0.4 on original scale) on some easier songs (song-specific results vary). The model learns spectro-temporal patterns and demonstrates reasonable segment-level accuracy, but shows bias (systematic overprediction of VA by 0.3–0.4 units on some songs) and larger errors on valence than on arousal. The model's end-to-end spectrogram learning captures timbre and short-term temporal patterns better than very shallow baselines; it's simple to implement and efficient to train relative to large LLMs. The model's simplicity continues to provide benefits because it trains quickly and runs light while delivering acceptable results and segment-wide performance that outperforms 12

complex systems and massive LLM-based models. The model's short-time window restricts its ability to detect extended emotional changes so researchers should explore adding recurrent layers or attention mechanisms or transformer-based temporal processing to mel-based input systems. However, it lacks explicit lyric modeling and higher-level semantic understanding; performance varies across songs and suffers from label noise and class imbalance when converted to discrete labels. CNNS like those in Dylan7e [2025] are a strong low-to-mid baseline for VA regression and illustrate the benefits of spectrogram-based end-to-end learning, but they are insufficient by themselves to achieve the best valence/arousal classification without text. Cross-comparison of the 3 models: Accuracy ceiling and complementarity of the modality. Measured on the same VA → discrete labeling scheme, lyric LLMs outperform simple audio-feature classifiers for lyric-heavy, metaphorical songs (50 percent vs. 40 percent); CNN-based regression (Dylan7e [2025]) shows competitive continuous VA recovery (RMSEs consistent with recent MIR work) but without lyrics struggles with valence classification once VA is discretized. The practical ceiling for single-modality systems is therefore dependent on modality: audio models reach higher accuracy and confidence on arousal, lyric models on word-driven valence distinctions. Valence vs arousal as modeling targets. All three systems corroborate the statement: arousal is easier to recover from acoustic patterns (tempo, RMS, high-frequency energy), while valence depends on lyrics, longer context, and cultural norms. Accordingly, regressing continuous VA (as Dylan7e [2025] and Chandrasena M.M.D. [2023] do) preserves nuance and lends itself to tasks like affective trajectory modeling, while discrete classification into categories may be less accurate. Supervised vs

unsupervised / zero-shot tradeoffs. Supervised audio models (Chandrasena M.M.D. [2023], Dylan7e [2025]) learn task-specific mappings from acoustic inputs to continuous VA and typically produce better-calibrated probabilistic outputs when trained with enough labeled data. Zero-shot LLM lyric classification offers quick lyric generalization without labeled music data but is vulnerable to prompt sensitivity, class imbalance, and calibration drift. A hybrid workflow—use supervised VA regression for advanced audio signals and LLMs for semantic enrichment and uncertainty estimation—produces the most practical path toward higher end-to-end accuracy. Calibration and interpretability. Calibration diagnostics (ECE, Brier-style measures, confidence–accuracy plots) reveal that audio models can be well calibrated with after-thefact techniques, while LLMs provide richer rationales that improve interpretability even when their raw confidence requires correction. Using both modalities together and reporting calibration allows for more reliable MER systems suitable for applications (therapy, recommendation, automatic tagging).

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2.8. Metrics And Loss Functions Psychologists use valence (see Definition 1.1) and arousal (see Definition 1.2) as two different dimensions to study affective states: valence measures unpleasantness to pleasantness (negative to positive) and describes the experience hedonic value, while arousal measures the level of excitement and tracks physiological responses and attentional involvement. (Russell [1980]). The emotional quality of valence determines whether an experience feels positive or negative, guiding our decision-making and behavioral responses between approaching or avoiding things. The arousal dimension shows how much nervous system activity and attentional focus occurs, which determines reaction speed and memory retention power and physical responses like heart rate and skin conductance. (Picard [2000]). The circumplex model presents valence and arousal as its two fundamental axes which create a continuous 2-D space where specific emotional labels such as “happy” and “angry” exist in distinct quadrants.

Figure 13: Russell’s Circumplex Model. Emotions can be mapped with continuous values as shown by the words in each isolated point, or as discrete labels, representing a broader emotion. Emotional geometry shows that high-arousal emotions can be negative like panic or 14

positive like excitement (Russell [1980]). The experimental behavior of dimensions depends on how the research is conducted. The IAPS picture set and other normative stimulus collections use independent ratings for valence and arousal to demonstrate typical ”boomerang” patterns in valence–arousal plots because strong valence stimuli do not always produce high arousal levels, thus requiring separate analysis of these valence and arousal (Lang et al. [1988]). The modeling approach of affective-computing pioneers supported the use of continuous valence/arousal representations because these representations provided better scalability for real-world systems than discrete emotion lists. The approach simplified annotation tasks and created direct connections between these representations and both physiological sensors and multimedia signals (Picard

[2000]). Research studies from recent years show that most datasets and models now focus on both axes yet they confirm that arousal prediction from physiological and acoustic signals outperforms valence prediction. The researchers believe this pattern exists because arousal shows direct relationships with measurable activation signals (EEG power bands and EDA and voice energy), whereas valence requires contextual understanding of subtle appraisal processes that are difficult to measure (Lian et al. [2023]). Analysis of DEAM music data and extensive speech and video collections reveals that human raters disagree more about valence ratings than arousal ratings, leading AI researchers to develop hybrid methods that combine multiple AI approaches for valence signal recovery (?).

3. Conclusion 3.1. Our Contributions We developed a multimodal LLM-based system for music emotion classification. Our model uses audio features extracted with librosa, such as tempo, spectral properties, and energy levels, in addition to the lyrics to classify emotions. We are able to examine both model behavior and calibration because the LLM produces an emotion prediction, a confidence score, and a natural-language explanation for every song. With this configuration, we can investigate how multimodal cues are processed by large language models and how well their internal logic matches human-interpretable emotional signals. We contextualize this system within a broader comparison across three levels of MER complexity. Compared with the low-complexity Dylan7e model, which relies on simple features and shallow learning methods, our LLM approach captures more nuanced emotional information, especially in cases where the lyrics carry sentiment that the audio alone cannot convey. Where the Dylan7e model tends to oversimplify ambiguous examples, our LLM's multimodal reasoning provides richer, more context-aware predictions. Against the medium-complexity Chandrasena CNN/BLSTM model, which focuses purely on audio, our approach benefits from integrating lyrics and higher-level descriptors that deep audio networks cannot infer. While Chandrasena's model handles broad valence and 15

arousal patterns effectively, it struggles with emotions that are in the lyrics that may be different from those in the audio. The LLM system fills this gap by grounding its predictions in both acoustic patterns and semantic content, producing more interpretable and fine-grained emotional distinctions. Together, these comparisons highlight the progression from simple acoustic modeling, to deep audio representation learning, to multimodal, reasoning-driven LLM-based emotion classification. Our study demonstrates how increasing representational richness influences model behavior and provides a clearer understanding of what different model classes can and cannot capture in the emotional structure of music. It's also important to keep in mind that when dealing with labels in data, it's important that they accurately reflect the nature of the data as well as possible. Self-created labels that act as the "ground truth" in an experiment can sometimes be inaccurate, causing the results and therefore the resulting conclusions to lose reliability. Therefore, there is always a factor of potential errors that occur from a labeled dataset that isn't completely representative of the emotions the songs express.

3.2. Limitations/Future Work 3.2.1

Multi-Lingual Models

In the future, we hope to repeat Chandrasena M.M.D. [2023]'s experiments in other languages, like Spanish, Russian, Chinese, etc. It'd be interesting to see how inguistics, phonetic variability and stress patterns affect models of varying complexities. It would also be interesting to see if the observed error patterns and calibration trends from English data appear in other languages through cross-lingual replication. We can also focus on enhancing both the reliability and precision of emotion labels found in Music4All, the dataset for our model. To make the model more accurate, the dataset can be re-annotated to reduce noise and ambiguity. We also hope to try and evaluate other calibration methods, such as temperature scaling and isotonic regression to establish if basic post-processing techniques can decrease model overconfidence in both audio and lyric prediction systems. The self-evaluation framework can also be expanded through additional scoring methods, like Brier scores. Limitations: First and foremost, our comparison lacks experiments that compare all three models under identical conditions. The authors of Dylan7e and Chandrasena published limited implementation details, so we needed to use their reported results instead of training their systems on a common dataset. Additionally, our LLM system used extracted audio features instead of using direct audio embeddings from raw audio data. Although this made things simpler, it prevented us from accurately testing more sophisticated audio. Furthermore, the LLM's output was very sensitive to the phrasing of our prompt, which means that even small wording changes could influence the predicted emotions and confidence levels. This means the data

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we collect can vary and could be a result of specific wording choices. Our study used English lyrics from Western datasets, which restricts its scope. The LLM's multimodal predictive abilities are still unknown for cultural and linguistic contexts outside of Western English-speaking areas. Lastly, our study wasn't able to evaluate model performance against other variables, like songs from different genres, which would have made our study more robust.

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C4 Gene Overexpression Drives Dopamine Imbalance in Schizophrenia Through Excessive Synaptic Pruning

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Abstract

excessive synaptic pruning Schizophrenia is a neurodevelopmental disorder that is present in approximately 1% of the population, and it significantly debilitates the person's quality of life.1 Studies show that nearly 10% to 13% of schizophrenic patients' cause of death is suicide. Schizophrenia usually exhibits itself in the late teens and early twenties of males, and late twenties to early thirties for females. The common symptoms associated with the disorder are characterized into the categories: positive and negative.2 Positive symptoms refer to behaviors which involve the decrease or absence of normal functions, which often include hallucinations, delusions, and incoherent thought. On the other hand, negative symptoms are amplified or distorted versions of normal behaviors. Negative symptoms involve the decrease or complete absence of normal functions related to motivations, emotions, and interest. Commonly, these symptoms are characterized by avolition, anhedonia, asociality, blunted affect, and alogia. While there are antipsychotic medications available for the treatment of schizophrenia, these medications tend to be more beneficial towards alleviating positive symptoms.3 Therefore, it is critical that the mechanisms underlying negative symptoms are better understood to improve subsequent treatment. Although the precise details of schizophrenic pathoetiology are unknown, extensive research has indicated that the disease involves the striatum and prefrontal cortex (PFC) regions of the brain, as these areas are essential for decision making, reasoning processes, reward processing, and impulse control. Such functions are essential for coherent reasoning and subsequent intended behaviors. In order for the striatal and prefrontal cortical regions to perform these functions, the neurotransmitter dopamine is required for synaptic signaling and neurotransmission by binding to and activating specific receptors on postsynaptic neurons to

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carry messages.4 Thus, when dopamine levels are imbalanced, this can lead to abnormal thoughts and behaviors. Antipsychotics modulate the amount of neurotransmitters like dopamine and serotonin available at the synapse.5 One aspect of how dopamine levels are regulated is through the connectivity of synapses. Microglial cells in the brain regulate synaptic pruning, to adjust neuronal connectivity and communication.6 Interestingly, in the striatum of patients with schizophrenia, dopamine levels have been found to be too high, whereas in the prefrontal cortex, there is a lack of dopamine. This causes subsequent hyperconnectivity in the striatum, and hypoconnectivity in the PFC. This connectivity between neurons is essential as it interlinks them into a complex web of neuronal circuits in the brain. Therefore, this review worked to examine the factor(s) that cause the elevation of dopamine in the striatum, and decrease of dopamine in the prefrontal cortex of patients with schizophrenia. Furthermore, it was determined that the C4 gene, a master regulator of synaptic pruning, and its variant forms of expression are responsible for the elevation of dopamine in the striatum and decrease of dopamine in the prefrontal cortex of patients with schizophrenia. In order to understand the general imbalance of dopamine levels throughout different regions of the brain in schizophrenia, it is essential to understand the role dopamine plays within the striatum and the prefrontal cortex. Understanding the mechanisms of the dopamine imbalance will better allow for potential treatments for this disease in the future.

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Elevation of dopamine in the striatum

In the striatum, the neurotransmitter dopamine is trafficked within synaptic vesicles between neurons to facilitate cell to cell communication. Dopamine is critical for striatum function, as it regulates the activity of neurons, which ultimately reinforce or renew neuronal connections. Dopamine modulates reward processing, movement, and motivation signals within the striatum, thus influencing various aspects of human thought and behavior. However, in order for dopamine to be able to signal messages between neurons, synapses must be plastic, such that they can either strengthen

or weaken in response to increases or decreases in activity,

respectively. When synapses have the ability to adjust the strength of connectivity between two neurons, this allows for proper cell signaling, communication, memory storage and learning. Consequently, when neuronal connections are too weak or unnecessary to the brain due to inactivation, these synapses and connections will be removed through pruning by microglia. Synaptic pruning is a common mechanism that the brain carries out to maintain itself efficiently and optimize neuronal circuitry. When this happens in excess, important signaling processes and connections are also cut off unnecessarily. In summary, when important neuronal connections are severed and synapses are unable to transmit signals, this results in a disturbance in the general neuronal circuitry of the brain, which relies on each region to manage specific processes. When neuronal connectivity is disturbed in a particular region, then those neurons will not have available synapses to connect and communicate with each other, thus affecting subsequent function associated with the region. Since the brain is a connected system which depends on each region to carry out normal functions, when one region of the system falls short, this will inevitably affect neighboring regions of the brain. Additionally, it is vital to recognize that in order for the striatum to be able to conduct motor movements, social interactions, cognitive tasks, and the reward process, it requires tight regulation of the exact quantity of dopamine available to neurons.7 Due to this tight regulation, both hypodopaminergic and hyperdopaminergic activity can be detrimental to neuronal circuits. When the situation of hyperactivity of dopamine arises in the striatum, such as in schizophrenia, Lorenzetti, V., & Cousijn, J. (2016). Striatum - an overview | ScienceDirect Topics. Www.sciencedirect.com. https://www.sciencedirect.com/topics/medicine-and-dentistry/striatum 7

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the natural biological response of the synaptic activity in the region will be to process whatever amount of dopamine is available by using the neurotransmitter to its maximum potential.8 In such a case, the reward process circuit signaling between neurons will consequently become dysregulated due to incorrect modulation of the neurotransmitter. This would then send invalid or overly amplified signals between neurons, reinforcing faulty circuit pathways. This is the reasoning as to why in schizophrenia, the reward process becomes so irregular, leading individuals to interpret stimuli in a disillusioned manner. In such a situation, the levels of dopamine in the striatal synapses would be too high, but the neurotransmitter will still carry out its function in modulating reward processes, facilitating hyperconnectivity within the region. Furthermore, this hyperconnectivity exacerbates striatal signaling and subsequent function, thus manifesting as irrational behavior such as distorted reward processes, decrease in cognitive ability, and flawed decision making.9 In short, dopamine elevation in the striatum causes the reward process to become faulty as a result of the dysregulated amount of this neurotransmitter.

Howes, O. D., Montgomery, A. J., Asselin, M.-C., Murray, R. M., Valli, I., Tabraham, P., Bramon-Bosch, E., Valmaggia, L., Johns, L., Broome, M., McGuire, P. K., & Grasby, P. M. (2009). Elevated Striatal Dopamine Function Linked to Prodromal Signs of Schizophrenia. Archives of General Psychiatry, 66(1), 13. https://doi.org/10.1001/archgenpsychiatry.2008.514 8

In accordance with the abstract of this paper, there is an apparent correlation between the negative symptoms manifestations and striatal reward processes' dysfunction. Juckel, G., Schlagenhauf, F., Koslowski, M., Wüstenberg, T., Villringer, A., Knutson, B., Wrase, J., & Heinz,

A. (2006). Dysfunction of ventral striatal reward prediction in schizophrenia. NeuroImage, 29(2), 409–416. https://doi.org/10.1016/j.neuroimage.2005.07.051 9

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Decrease of dopamine in the prefrontal cortex

Dopamine is essential for the PFC to facilitate neuronal connectivity and process interpretation of stimuli to other regions of the brain in order to perform its functions in reasoning, judgement, and cognition. When nerve impulses are transmitted from the prefrontal cortex to other regions of the brain, this bridges higher order critical thinking with subsequent emotional responses and associated behavior. In the brain of schizophrenic patients, a significant decrease in the levels of dopamine in the PFC has been observed in numerous studies. This is the result of hypoconnectivity between neurons in the region, as well as a preceding lack of synaptic density in the area. The hypoconnectivity within the prefrontal cortex is attributed to the combination of over-pruning of synaptic clefts in the region, as well as a lack of dopamine to modulate cell-to-cell signaling essential for decision-making and behavioral control. The reduction of normal levels of dopamine results in behavioral dysregulation in the schizophrenic brain. Dopamine deficiency drives the regional synaptic signaling to become unsynchronized, thus resulting in disruption of emotional processing and cognitive function. The depletion of dopamine in the PFC is strongly correlated with the severity of negative symptoms, suggesting that targeting the over pruning of synapses may reverse negative symptoms. Synaptic pruning in the PFC complicates neuronal dopamine release and reuptake, and is mediated by microglia. Microglia are cells tasked with maintaining the brain's neurons free of unnecessary connections, plaques, and even damage. Microglial cells maintain neuronal functioning properly by pruning damaged synapses on neighboring neurons. Although the exact source of decreased synaptic density in the PFC region of the brain is unknown, scientists have noted that this occurrence is present within other regions of the brain, including the striatum. This pattern being closely monitored to recur in multiple brain regions has led scientists to theorize that disrupted mechanisms of synaptic plasticity in schizophrenia can lead to a larger scale neuronal circuitry purging in the brain. Moreover, such a notable level of synaptic pruning in the brain overall, but specifically the

prefrontal

cortex,

further

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cognitive

dysfunction

for

schizophrenic

patients.10Overall, the combination of synaptic pruning, hypoconnectivity between neurons Okubo, Y., Suhara, T., Suzuki, K., Kobayashi, K., Inoue, O., Terasaki, O., Someya, Y.,

Sassa, T., Sudo, Y., Matsushima, E., Iyo, M., Tateno, Y., & Toru, M. (1997). Decreased prefrontal 10

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(diminishing plasticity) and the disruption of dopamine signaling (essential for the PFC to respond to certain classes of stimuli), leads to dysregulation of the region's ability to manage the functions of interpreting situations appropriately. Thus, when schizophrenic patients are unable to cooperatively reason and interpret any kind of stimuli they might encounter in their lives, this manifests as negative symptoms, namely avolition, asociality, anhedonia, and alogia.

dopamine D1 receptors in schizophrenia revealed by PET. Nature, 385(6617), 634–636. https://doi.org/10.1038/385634a0

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C4 Gene in synaptic pruning

While the molecular and cellular mechanisms underlying schizophrenia are yet to be fully understood, variations of the complement component 4 (C4) genes have been implicated in its pathoetiology. The C4 genes are associated with signaling microglia to prune synapses that are unnecessary or damaged in the brain.11 Several isoforms of C4 exist that vary based on molecular targets and size, but the most notable within the context of schizophrenia are C4A, C4B, and C4AL. C4A overexpression causes excessive synaptic pruning due to the excess production of complement immunoproteins that tag synapses for pruning by microglia in different regions of the brain. Synaptic pruning is a key mechanism of schizophrenia that underlies the loss of connectivity between neurons, and therefore the disruption of key pathways required for neurotransmitter signaling such as dopamine. Research has shown that this gene is expressed in both the prefrontal cortex and the striatum of patients with schizophrenia. However, despite the fact that both of these regions have the same gene being expressed, their subsequent signaling cascades result in different effects. Due to this phenomenon, it is highly plausible that the reason for the striatal elevation of dopamine, along with the simultaneous dopamine deficiency in the prefrontal cortex is the brain's unique response to ensuring homeostasis in each respective region.12 Dopaminergic neurons in the striatum may compensate for the excess of synaptic pruning as a result of the immunoproteins and microglia by increasing dopamine demand.13 Chen CC, Howie J, Ebrahimi M, Teymouri K, Woo JJ, Tiwari AK, Zai CC, Kennedy JL. Analysis of the complement component C4 gene with schizophrenia subphenotypes. Schizophr Res. 2024 Sep;271:309-318. doi: 10.1016/j.schres.2024.07.039. Epub 2024 Jul 30. PMID: 39084106. 11

Because each region of the brain is so specialized and matched to an exclusive function, this

results in distinct neurophysiological and structural differences. Stansberg, C., Audun Osland

Vik-Mo, Holdhus, R., Harald Breilid, Srebro, B., Petersen, K., Jørgensen, H. A., Jonassen, I., & Steen, V. M. (2007). Gene expression profiles in rat brains disclose CNS signature genes and regional patterns of functional specialisation. 8(1), 94–94. https://doi.org/10.1186/1471-2164-8-94 12

Rey, R., Suaud-Chagny, M.-F., Bohec, A.-L., Dorey, J.-M., d'Amato, T., Tamouza, R., & Leboyer, M. (2020). Overexpression of complement component C4 in the dorsolateral prefrontal cortex, parietal cortex, superior temporal gyrus and associative striatum of patients with schizophrenia. Brain, Behavior, and Immunity, 90, 216–225. https://doi.org/10.1016/j.bbi.2020.08.019 13

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However, excessive pruning in the prefrontal cortex due to overexpression of C4 may not elicit a compensatory neurotransmitter response, thus causing the deficit of dopamine as is observed in patients with schizophrenia. In summary, the effects of schizophrenic pathoetiology can likely be attributed to the related schizophrenia gene C4 and its variants, which overprune essential synapses in regions of the brain. This consequently disrupts homeostasis and signaling in and between the striatum and prefrontal cortex. These disruptions to synaptic plasticity and dopamine cause the striatum and prefrontal cortex to respond differently, creating the imbalance of dopamine expression in these two regions in the schizophrenic brain. These findings suggest that the C4 gene exacerbates the deficits in neuronal connectivity throughout the brain, leading to positive and negative symptoms observed in schizophrenia.

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Conclusion

Overall, the C4 gene mediates dopamine dysregulation in both the striatum and prefrontal

cortex through different mechanisms.The elevation of dopamine in the striatum for schizophrenic patients, alongside synaptic pruning as a result of C4 overexpression, leads to striatal dysregulation. When the striatum faces hyperdopaminergic expression in its synapses, this disrupts the ability of the striatum to control essential functions like the reward process system. The failure to control such functions in the striatum results in the manifestation of symptoms such as delusional beliefs. Furthermore, the combination of hypodopaminergic activity and excess pruning of synapses in the prefrontal cortex leaves the region unable to modulate behavioral and physical responses to stimuli, ultimately leading to altered thoughts and behavior. Since the prefrontal cortex requires dopamine to communicate signals between neurons for regulation of emotion and behavior, the lack of the neurotransmitter would result in symptoms like blunted affect and avolition. The effects of schizophrenic pathoetiology can likely be attributed to the related schizophrenia C4 gene causing overpruning of essential synapses in regions of the brain, consequently disrupting the homeostatic balance of dopamine, neuron connectivity, and signaling in the striatum and prefrontal cortex regions. The striatum and prefrontal cortex likely respond to such deficits in different manners, which explains the simultaneous elevation of dopamine and decrease in dopamine, respectively. Pinpointing a cause of the biological mechanisms behind schizophrenia can help to create

treatment options in the future. Some limitations in this research include the fact that there is more widespread research and findings involving the role of the prefrontal cortex in schizophrenia than the striatum. Additionally, research connecting neuroimmunology and

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genetics to schizophrenia (specifically the C4 gene) is still very new in the field. Future investigation into the specific role of C4 in the striatum and prefrontal cortex will be necessary to further understand the different responses of dopamine signaling. Another limitation is that current animal models for schizophrenia inhibit the measurability of irrational behavior and symptoms observed in humans. Taken together, we can better understand the complex mechanisms driving schizophrenia, thus leading to potential drug targets or therapeutic treatment in the future.

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The Effect of Social Media on the Mental Health of Older Adults

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Abstract

With the rapid growth of technology and the internet, social media has established a significant presence in the lives of all. As of 2023, there are 4.8 billion social media users worldwide, making up nearly 59.9% of the global population [1]. Social media is a general term for websites and applications that enable users to create, share, and participate in online social networking. Active social media use occurs when users directly interact with the platform, such as commenting on a post or sharing online content. On the other hand, passive social media use occurs when users consume and view media on platforms without directly engaging with it. The impact of social media on a person's mental health will vary depending on their unique use of the platforms [2]. Research shows that social media can cause anxiety, depression, sleep disruption, and emotional volatility, all of which engender side effects like memory issues, headaches, and an overall lower quality of life [2]. Thus, it is critical to better understand the relationship between social media and mental health.

Currently, the majority of social media research focuses on the younger generations, mainly adolescents and young adults, leaving unanswered questions about its impact on the older generations (65+ years). However, addressing this research gap is essential because older generations use social media for different purposes and have different brain functioning and cognitive processes that influence their psychological impact. Current literature will not account for the discrepancy between the two generations. Additionally, as one grows older and physical health declines, social media may be the most convenient way to socialize. This natural dependency on a digital community may have consequences not yet seen in studies of adolescents.

This review will focus on the impact of social media on the mental well-being of the older generation. It will also include information about the younger generation to highlight the differences between the two. Due to the different focuses of studies investigated in this review, some data are limited to certain platforms, such as WeChat or Facebook, and have taken place in different locations, each with its unique social and environmental factors that may engender discrepancies between the results. We will provide a well-developed summary of existing knowledge about the impact of social media on the older generation. This review will focus on the impact of social media on the older generation to ultimately answer the question: How does social media affect the mental health of older adults?

2 The Positive Impact of Social Media on Mental Health

According to numerous studies, social media usage is positively linked to better mental health in older adults by reducing perceived loneliness, making communities accessible, allowing self-expression, and promoting cognitive engagement. Social media allows older adults to maintain their social roles, participate in a complex society, and promotes a more active life [3]. These positive aspects all promote the well-being and health of the older population [3]. In this section, we will further discuss the benefits of social media to the well-being of older adults.

2.1 Reducing Loneliness and Enhancing Community

As a social species, social connections play a crucial role in preventing mental health issues and promoting overall well-being. On the contrary, social isolation has been associated with poorer mental health, causing increased prevalence of depression [4]. The association between loneliness and depression applies across all generations, but technology-based interactions are effective in reducing loneliness specifically among older adults. [4]. Factors that typically increase a person's risk of social isolation include loss of mobility, sensory loss, cognitive decline, retirement, financial struggles, and technological illiteracy [5], all of which are common in older adults. In short, social media benefits the mental health of older adults by reducing social isolation and providing an accessible community [3].

As its name suggests, social media refers to web-based applications that promote the creation and exchange of user-generated content [6]. By allowing users to post pictures, upload videos, share ideas, and interact with each other through video chatting and messaging, social media platforms enable users to create and maintain interpersonal relationships. The online nature of these interactions is beneficial for older adults, especially those with mobility impairments or a lack of transportation that makes in-person interactions difficult. Mobility limitations are becoming increasingly common in older persons and have been associated with poor psycho-social health, affecting nearly 35% of people aged 70 and the majority of people over 85 years of age [7]. Thus, social media provides a means of communication that does not require one to be physically present, offering a way to decrease loneliness and foster community for mobility-impaired older adults.

Another way in which social media reduces loneliness is by fostering intergenerational relationships [8]. Regular interaction with the younger generations provides companionship and cognitive stimulation, combating the isolation that accompanies retirement, loss of loved ones, or limited mobility [8]. In multigenerational programs, older adults who engage with youth report decreased social isolation, greater life satisfaction, and heightened cognitive functioning [9]. Since younger people tend to be more active in society – through work, school, traveling, and technology – intergenerational relationships allow older adults to learn from diverse perspectives and feel more integrated in modern society. In general, social media offers the support and social connection needed to cope with stress, anxiety, and depression, providing emotional and even physical benefits [10].

2.2 Self-Expression and Identity

For all users, social media offers an outlet for self-expression and identity. Though most users find it tempting to curate an idealized, less-realistic version of themselves to garner validation from others, research finds that authentic self-expression benefits well-being and overall happiness [11]. When users post about their opinions or join an online community, they not only contribute to the larger community but also explore their own identity. In this case, older adults can feel a sense of belonging and validation by joining a community, while developing their identity through exposure to other ideas.

In order to express oneself on social media, active social media use is required. Active social media use is when users directly engage with the platform through liking posts, sharing pictures, and communicating with others. For older adults, active social media use benefits mental health by decreasing perceived loneliness and encouraging greater participation in a community [12]. A study on the Chinese social media platform WeChat found that actively posting pieces of

personal life on the platform improved symptoms of depression, self-rated health, and health satisfaction of older adults [13]. Sharing opinions within a community united by shared interests allows an individual to feel included, build relationships, and deepen their beliefs. Joining communities with contrary opinions exposes individuals to different perspectives, enabling them to stay open-minded and deepen the breadth of their knowledge [14]. In conclusion, the social inclusion, engagement, and growth experienced from using social media as a platform for authentic self-expression and identity can benefit the mental well-being of older adults.

2.3 Cognitive Functioning

According to the American Psychological Association, cognitive functioning is the performance of mental processes like perception, learning, memory, awareness, reasoning, and more [15]. Poor cognitive function is an indication of poor psychological well-being, particularly stemming from mental health disorders such as depression [16]. A major consequence of a decline in cognitive functioning is dementia, a broad term for symptoms marked by a decline in brain function severe enough to interfere with daily life [17]. In 2021, 57 million people worldwide had dementia, with the majority of patients being 65 years of age or older [18]. A major contributor to dementia is social isolation, which can be combated with productive social media use [19].

A study on participants of an average age of 75.85 years found that stopping the use of the internet, technology, and social media is linked to cognitive decline, measured by executive function and memory [20]. Older adults who regularly used computers in their own time performed better on executive function tests, which assessed problem-solving, reasoning, and planning skills [20]. Those who were exposed to more information and communication technologies also had better episodic memory over time [20]. This is because navigating and utilizing technology requires tasks like active recall, recognition, and memory [20]. Therefore, social media use may help reduce the risk of various mental health problems like dementia and depression in older adults by improving cognitive functioning.

3 Negative Impact of Social Media on the Mental Health of Older Adults

Currently, there is no consensus about the negative effects of social media on the mental health of older adults. Most existing research focuses on social media's impact on the mental health of adolescents and young adults, showing that excessive social media use is linked to higher rates of anxiety, depression, and overall poorer well-being ^(21,22). This association can be explained by cyberbullying, negative social comparison, and the replacement of in-person interactions with online ones — all of which can increase the risk of anxiety and depression ^(23–25). However, these results do not apply to older adults because they are less likely to engage in social comparison and social media in general ^(26–28). Based on our limited analysis of current research, social media has generally been described as having a net positive impact on the mental health of older adults.

Studies that do indicate a positive association between social media and depressive symptoms are not sure about its causation, as it is possible that older adults who already experience poor mental health turn to social media as a substitute for social interactions, increasing isolation [29]. Still, there are clear risks that social media poses to the mental health of older adults. Thus, in this section, we will highlight the main risks that social media poses to the mental health of the older generation.

3.1 Misinformation and Online Scams

Social media can negatively affect the mental health of older adults by exposing them to misinformation, targeted scams, and overwhelming digital content, causing anxiety, confusion, and shame. In a survey of UK adults, nearly 61% of older adults have been the target of financial fraud, with 17% falling victim [3O]. Older adults are especially susceptible to believing and sharing the most misinformation, which has increased with the growing sophistication of internet scams ^(31,32). After being deceived, victims of internet scams report feeling shame, guilt, anger, helplessness, and fear, all of which can cause anxiety, depression, post-traumatic stress disorder, and suicidality [33].

Consequently, older adults are more at risk of falling victim to online scams, which is positively correlated with depression [28]. Fraud prevalence is three times higher among older adults with higher rates of depression and lower social-needs fulfillment than those with stable mental health and a solid social system [34]. Due to their susceptibility to misinformation, older adults are more at risk of being deceived by scams on social media, which is an indicator of depression. To sum up, the victimization of older adults to misinformation and scams on social media platforms worsens their mental health by causing feelings of shame, helplessness, and guilt that can give rise to certain mental health conditions [33].

4 Compared to the younger generation: the Impact of Social Media on Mental Health

Although social media can impact the mental health of all age groups, its effects differ significantly between the younger and older generations. This discrepancy can be attributed to differences in brain development, social needs, and use of social media. During adolescence, the prefrontal cortex—responsible for social behavior, prioritization, and rational decision-making—undergoes significant development ^(35,36). Teenagers prioritize social relationships and validation, tending to turn towards social media to fulfill this desire [36]. Evidently, about 95% of youth ages 13-17 years report using a social media platform, with more than a third claiming almost constant use [37]. Along with ongoing changes in the brain and body, teens are more likely to experience mental health problems—mainly anxiety, depression, and eating disorders [36].

In contrast, about 45% of those aged 65 and older report using social media, expressing uncertainty about the utility and relevance of technology to fulfill their current priorities and needs ^(38,39). Older adults also report language and technology illiteracy and face ageist stereotypes that hinder sustained use [39]. Social media has proven to be a double-edged sword that can provide both positive and negative effects depending on the individual's personal use of the platform: passive versus active or occasional versus frequent [4O]. In this section, we are going to compare and contrast the impact of social media on the mental health of the younger and older generations to highlight the risks, benefits, and patterns between the two.

4.1 Social Media's Positive Impact on the Younger Generation

To start, social media can provide mental health benefits to the younger generation through social connection [41]. Essentially, social media provides an online space where individuals can join communities, communicate with others, and share content; thus, it enables adolescents to keep in touch and establish connections with friends, family, and users with similar interests [42].

During the COVID-19 pandemic lockdown, which limited in-person interaction and education, social media helped adolescents maintain social connections [43]. In particular, video chatting, a feature on most social media platforms, was associated with lower levels of perceived loneliness and lower depressive symptoms [44]. Besides the pandemic, multiple studies emphasize

that active participation on social media, such as engaging with posts and chatting with users, is associated with reduced loneliness, while passive use, such as scrolling through videos without engagement, does not provide the same benefit [42]. These benefits are similar to those seen in older adults. Social media platforms offer accessible digital communities for older adults, reducing perceived social isolation [3]. Ultimately, social media can have a beneficial impact on the mental health of both adolescents and older adults by providing means to attain social connections.

Additionally, social media offers an outlet for an individual's identity and a way to connect with other users who share similar identities—a factor that accompanies an active use of social media. Expressing one's authentic self through personal or creative posts benefits the overall well-being and happiness of adolescents and older adults [11]. Especially for younger individuals of marginalized identities, social media can offer opportunities for identity exploration and affirmation, including ways that may not be feasible offline due to unsupportive family dynamics, cultural norms, or geographic isolation [45]. The anonymous and online aspect of social media encourages marginalized adolescents to express their identity more genuinely and freely. The exploration of identity is a key developmental task during adolescence and early adulthood [46]. Joining a community where one's personal identity can be expressed freely not only boosts a sense of belonging but also helps adolescents develop their identity and hear from the experiences of others. Although these findings are primarily stated regarding adolescents, they also apply to older adults. Social media encourages older adults to establish and grow their personal identity, which heightens self-esteem and overall happiness through external validation[14].

4.2 Negative Impact of Social Media on the Mental Health of Adolescents

Though social media can provide certain mental health benefits for adolescents, it can also damage their mental well-being. Social media in general allows both adolescents and older adults to share posts, interact with other users, and consume entertaining content. These features, however, leave users vulnerable to social comparison, cyberbullying, and addiction [47]. According to existing research on the younger generation, mainly adolescents and young adults, an excessive use of social media contributes to an increased risk for mental health symptoms, anxiety or depression diagnoses, and poorer well-being ^(21,22). This association may be due to the practice of replacing face-to-face interactions with digital ones, which can lower enjoyment during in-person interactions, increasing social isolation [25]. Additionally, cyberbullying and negative social comparison can increase the risk of anxiety and depression in younger adults ^(23,24).

However, as people age, they are less likely to engage in social comparison and social media in general ^(26–28). Therefore, social media has generally been described as having a net positive impact on the mental health of older adults while having an overall harmful impact on that of adolescents.

5 Conclusion

In this review, we compiled information from various research papers to answer the question: How does social media impact the mental health of older adults? Overall, the findings show that social media can leave a positive impact on the mental health of older adults by providing a means to connect with other users. Having accessible, digital social connections reduces loneliness, increases one's sense of community, encourages self-expression and exploration of identity, and improves cognitive functioning. Regarding the negative effects, current research does not provide a clear answer to how social media can harm the mental health of older adults. Still, we

found that social media could pose a risk to the mental well-being of older adults through exposure to misinformation and online scams, as older adults make up the majority of the victims, increasing anxiety and depression. Finally, compared to the younger generation, older adults experience more positive than negative effects from social media on their mental health, while adolescents experience the reverse. Due to differences in brain development, priorities, and use of social platforms, social media has vastly different impacts on the two generations.

This research matters because it examines the effects of social media on an overlooked population: older adults. Though social media's effects on younger users are extensively documented, there is far less known about how these platforms shape the mental health of older users. Importantly, this paper highlights the lack of research on the negative impact of social media on older adults. As the current generation of people who grew up with social media grows older, it is essential to examine its mental health effects on the older generations. Given the unique living situations and health conditions of older adults, it is necessary to expand current research to provide better care and mental support. More than ever, social connection is a priority for the safety and mental well-being of older adults, and curating better online environments can help them achieve this need.

This research paper has several limitations to consider before interpreting its findings. For one, we experienced restricted access to certain research papers, which, as a literature review, may have decreased the comprehensiveness of information presented. On top of that, in media studies, there is far less research on older adults than on younger generations, making it even more difficult to compile a whole review. As with most psychological studies, the majority of the data used may be biased by self-reporting. For instance, questionnaires and surveys may not accurately reflect the mental state of the respondent due to inaccurate self-perception or memory issues. Also, some researchers hold different definitions of an "older adult", with some determining an "older adult" as anyone above the age of 18. Differences in social media platforms, usage types, geography, and the population from which the data was extrapolated may also leave some points prone to discrepancies. For example, some studies use WeChat as the platform of focus, while others focus on Facebook or YouTube. These platforms provide different means of interacting with users and with the application, which have varying effects on the users. Finally, a lack of longitudinal research on this topic makes it difficult to identify causality and long-term observations.

For future studies, we recommend further research on the possible negative effects of social media on the mental health of older adults. Conducting a longitudinal study on social media's impact on the younger generation and observing its differences as the individual ages may offer more insight into early prevention of mental health disorders. To address the discrepancies between different social media apps (e.g., YouTube, Facebook, WeChat), we recommend more studies that either focus on one or compare multiple platforms and determine the unique benefits or disadvantages of each. To create safer online environments for the growing population of older adults on social media, it is crucial to note the aspects of these platforms that benefit or harm the mental health of older adults and take action to expand the current literature. Taken together, this paper points to the need for greater representation of older adults in digital media and psychological research, and for their needs to be fully incorporated into future research on the effects of social media on the mental well-being of older adults.

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Polycystic Ovary Syndrome and Its Effects on Women Based on Ethnicity

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Abstract

Polycystic Ovary Syndrome, or PCOS, is a common hormonal disorder affecting approximately 4-21% of reproductive age women globally (Lizneva et al., 2016). According to studies, PCOS is the main cause of infertility and oligoanovulation (consisting of oligo-ovulation and anovulation), the inability or irregularity of an egg releasing respectively ("Ovulatory Disorder", 2024), and can cause severe health complications if left untreated. Though the exact cause of PCOS is unclear, experts have proven that higher levels of certain hormones, including androgen, Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), and insulin are PCOS indicators (Huffman et al., 2023). PCOS mainly affects a component of the ovaries specifically, follicles that are trapped in the first stages of development as a result of hyperandrogenemia (Meczekalski, 2023). Hyperandrogenism is when there is an excess of androgen in the body. In women, this can lead to excessive hair growth, acne and irregular periods. ("What… Hyperandrogenism", 2025). Different polymorphisms are created through polygenetic mutations which affect these hormone levels resulting in multiple PCOS phenotypes based on specific comorbidities and symptoms. While there has been some research done on PCOS leading to therapeutics that aim to alleviate symptoms, there is still no specific cure for the condition. PCOS and its phenotypes are mainly diagnosed through the Rotterdam criteria (though other criteria for diagnosis do exist) which requires for the following attributes to be present: oligo-anovulation, hyperandrogenism, and polycystic-appearing ovarian morphology on ultrasonography (Christ and Cedars, 2023). However, despite this criteria, around 70% of women around the world are still undiagnosed (Yasmin et al., 2022), suggesting a need for more precise diagnoses. The diagnosis and treatment of minority groups especially is important to study as PCOS is more prevalent and presents differently between ethnicities. More research on the variations of PCOS associated medical conditions, especially in patients of different ethnicities, could lead to specialized therapeutic targets. The objective of this paper is to research the extent that genetic mutations affect the variations and presence of these comorbidities and medical conditions for different ethnicities across the globe.

Genetic and Hormonal Basis of PCOS

The dysregulation of hormone production from genetic mutations that lead to the development of PCOS have different phenotypes. There are 19 different risk gene loci for PCOS which are in metabolic, neuroendocrine, and reproductive pathways. (Hoeger, 2020).

PCOS Phenotypes

There are four phenotypes of PCOS commonly expressed, each with their own attributes, identified through ultrasounds (Khan et al., 2019).

Table 1-PCOS Phenotypes based on oligo-anovulation, hyperandrogenism, and presence of poly-cystic ovaries:

Phenotype	Numerous Poly-Cystic Ovaries	Oligo-anovulation	Hyperandrogenism
A	Yes	Yes	Yes
B	No	Yes	Yes
C	Yes	No	Yes
D	Yes	Yes	No

Poly-cystic ovarian morphology (PCOM) consists of multiple small sacs filled with fluid and eggs that have not yet been matured and can be seen as cysts when medical imaging is conducted. (“PCOS”, 2025). It has been found through studies that Phenotype A is the most common phenotype of PCOS while Phenotype D contains the most mild symptoms (Sachdeva et al., 2019). Phenotype A consists of numerous polycystic ovaries, oligo-anovulation, and hyperandrogenism, while Phenotype B has a normal appearance of ovaries, oligoanovulation, and hyperandrogenism. Both of these are classic phenotypes of PCOS, meaning Phenotypes A and B consist of more menstrual dysfunction, and higher levels of insulin resistance (Khan et al., 2019). In addition to the characteristics described in the table, Phenotype A also contains a higher LH/FSH ratio and higher risks of obesity (Lizneva et al., 2016). Phenotype C, or Ovulatory PCOS, consists of polycystic ovaries with regulated periods and hyperandrogenism. Ovulatory PCOS patients tend to have higher amounts and levels of serum insulin, androgen levels, and hirsutism scores (Khan et al., 2019). Finally, Phenotype D, or Nonhyperandrogenic PCOS, consists of polycystic ovaries, oligoanovulation, but with hyperandrogenism not present. Phenotype D has elevated endocrine levels and regular androgen levels (Khan et al., 2019). Elevated endocrine levels include a higher level of sex-hormone binding globulin, a protein involved in regulating the location and function of sex hormones (“Globulin”, 2025), as well as a low LH/FSH ratio, and low Triiodothyronine (T3) and Thyroxine (T4) levels, all caused by mutated hormonal genes (Kumar et al., 2016).

Genes and Polymorphisms

Hormonal mutations occur throughout the body that contribute to the development of PCOS. Specific genes are affected by polymorphisms, the presence of two or more variant forms of a specific DNA sequence, changing the expression and function of the gene itself (Gunter, 2025). Two well-studied areas of polymorphisms in regards to PCOS are hormones and the mitochondria. Mitochondrial dysfunction especially is a hub for genetic mutations for hormones regulating the endocrine system in the body. Mitochondrial dysfunction relates to the development and progression of PCOS (Dabravolski, 2021). Mutations in the mitochondria, such as dysregulated mitophagy (the inability to remove damaged mitochondrial cells leading to increased stress levels and lower energy levels), decreased ATP levels, and released Reactive Oxygen Species (ROS) all contribute to PCOS symptoms. Primarily obesity, insulin resistance, and metabolic syndrome, which is a cluster of factors such as obesity, high blood pressure, and low cholesterol which create a higher risk of heart diseases or stroke. ROS (reactive oxygen species), a byproduct sourced from the mitochondria, causes damage to mitochondrial and nuclear DNA, lipids, and proteins which can cause hormonal disorders such as PCOS. (Dabravolski, 2021). Most hormonal genes, such as CYP19, can be associated with a higher susceptibility to PCOS when polymorphisms such as SNP rs2414096 affect the gene. Studies have shown how the rs2414096 polymorphism can indicate

PCOS through the presence of hyperandrogenism, specifically in Iraqi women (Kaur et al., 2018). Specific alleles within these polymorphisms are what can change the genetic buildup of a hormone. For example, A and C alleles in rs12970134 and rs17782313, are the risk alleles associated with a high Body Mass Index (BMI) in Saudi Arabian PCOS women (Batarfi, 2019). Through certain genes mutated from polymorphisms, such as the CYP19 gene specifically affected from the rs2414096 polymorphism, chances of PCOS become higher through hormonal changes. These hormone imbalances can cause certain comorbidities/medical conditions. However, because thousands of polymorphisms exist, different variations of the same comorbidity can exist, and certain comorbidities can be present in some patients and omitted in others depending on factors, such as ethnicity. These are examples of polymorphisms that have been identified and associated with a particular PCOS phenotype within an ethnic group. More research on other polymorphisms could impact the possibility of specialized therapies and potential medicines for future patients, especially those that are specific to certain ethnicities.

Ethnicity in Relation to PCOS Comorbidities and Conditions

As PCOS is still being researched thoroughly, certain comorbidities tend to be more common, both in women with PCOS overall, and also in certain ethnicities. Some may be present in one ethnicity or race but not in another. Studies have found that globally, some common comorbidities and medical conditions that present themselves in PCOS patients are: hirsutism, insulin resistance and obesity, metabolic syndrome (including high blood pressure and hypertension), as well as infertility. Many ethnicities have higher or lower prevalence of these conditions, or simply lack the condition completely. Black, Hispanic, South Asian, Middle Eastern, White, and East Asian patients were most frequently associated with the following conditions (Sendur and Yildiz, 2021), however these comorbidities and conditions are not limited to just these specific ethnicities.

Hirsutism

Hirsutism is the excess of hair growth on parts of a patient’s body. The way that hirsutism is measured within patients is through the modified Ferriman-Gallwey (mFG) visual four-point scale (Sendur and Yildiz, 2021). The scale rates hirsutism from a level of 0 to 36, with 0 being minimal hirsutism and 36 being the highest level of hirsutism. Middle Eastern, Mediterranean, South Asian, African American, and Hispanic women with PCOS have been identified to have higher levels of hirsutism, than East Asian, Native American or White (Finnish, Norwegian, and United States) women (Afifi et al., 2017; Sendur & Yildiz, 2021). The differing levels of hirsutism have been led back to higher levels of the enzyme 5-α reductase, which produces androgens in the body, also contributing to hyperandrogenism (VanHise et al., 2023). Ethnicities with higher levels of the enzyme are more prone to hirsutism while those with lower levels are less prone. East Asian women have been found to have a significantly low 5-α reductase activity likely contributing to their reduced severity of hirsutism (VanHise et al., 2023).

Insulin Resistance and Obesity/BMI

Patients with PCOS tend to have 27% less insulin than normal (Huffman et al., 2023). Insulin resistance is typically measured by the rate of glucose metabolism in patients. In a study conducted on how Indian patients' hormonal levels are affected by PCOS, they had a higher prevalence of insulin resistance (Kumar et al., 2016), which could be led back to higher glucose concentration levels. Hispanic, Middle Eastern, and Black patients are prone to higher insulin

resistance as well, also because of increased glucose concentration (Sendur and Yildiz, 2021). Obesity in relation to PCOS is a complex process and relies on factors such as increased insulin resistance. In comparison to White patients, Black and Hispanic patients were more prone to obesity and increased BMI while South Asian and East Asian patients were less prone to increased BMI, though South Asian women still have a higher risk of obesity as well due to higher insulin resistance as mentioned (Sendur and Yildiz, 2021). Note that though genetic mutations play an important role in the development of these conditions, other factors such as economic status and environment also have a significant role.

Metabolic Syndrome (High Blood Pressure & Hypertension)

As mentioned, metabolic syndrome is a combination of factors that lead to increased risk of heart diseases and strokes ("Metabolic Syndrome", 2025). South Asian and Norwegian patients especially have been found to have an increased risk of developing metabolic syndrome; Norwegian patients especially despite lower obesity and/or insulin resistance levels (VanHise et al., 2023), which are two main factors for metabolic syndrome. More research must be conducted to identify the specific reason, however the likely conclusion is outside factors such as environment and diet. Blood pressure and hypertension are also two important and prevalent factors when identifying metabolic syndrome in PCOS patients. Non-Hispanic Black patients specifically have been found to be more prone to higher blood pressure and hypertension, both key components of metabolic syndrome (VanHise et al., 2023). Hypertension increases cardiovascular morbidity and mortality. (Stanciu et al., 2023). However, in comparison to Hispanic patients, Non-Hispanic Black patients had a lower level of metabolic syndrome (Engmann et al., 2017). White European and White American patients were also prone to higher blood pressure than East Asian, South Asian, and Middle Eastern patients (Sendur and Yildiz, 2021). Overall, certain ethnicities are more susceptible to specific factors, within the conditions of metabolic syndrome.

Infertility

About 70% of patients are infertile because of having PCOS (Ajmal et al., 2019). Studies have found that the CYP11A1, CYP17A1, and CYP19A1 genes, when mutated by polymorphisms, can significantly increase the chance of infertility when PCOS is developed in a patient's body (Heidarzadehpilehrood et al., 2022). In Indian patients with PCOS, through studies done, there was a statistically significant prevalence of the mutated CYP11A1 gene in North Indian as well as Greek patients (Heidarzadehpilehrood et al., 2022). The CYP11A1 gene when mutated from the rs4077582 polymorphism produces a higher level of testosterone, as well as a higher amount of androgens (Heidarzadehpilehrood et al., 2022). Moreover, there were also higher levels of prolactin in Indian patients, which can cause irregular periods when at elevated levels (Kumar et al., 2016). These hormonal imbalances can therefore cause anovulatory infertility in patients.

Ethnicity can also be a factor for the phenotype of PCOS as well. For example, Hispanic women are prone to have Phenotype A of PCOS with the most comorbidities, when speaking in terms of hyperandrogenism and metabolic criteria (Engmann et al., 2017). On the contrary, Black, non-Hispanic, women have milder PCOS symptoms than Hispanic women and sometimes, non-Hispanic white women (Engmann et al., 2017), making them more prone to Phenotype D. Certain ethnicities also have higher rates of having PCOS than others, which should also be taken into consideration. Japan, New Zealand, and Brunei Darussalam, when studied, had the highest rates of PCOS, particularly among women aged 20–24 years and 25–29 years of age (Jiang, 2025). Japan especially had a higher incidence rate above 400 for every 100,000 women ranging from age 20-24

(Jiang, 2025). Ethnicity plays a key role in identifying a patient's comorbidities and is therefore essential to understand to find and prescribe proper treatment and therapeutics.

Diagnosis and Treatment

Current Methods of Diagnosis

As previously mentioned, currently, the main form of diagnosis for PCOS is the Rotterdam Criteria. This criteria calls for two of the three following characteristics to be present: hyperandrogenemia and/or hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology, to be diagnosed with PCOS (Christ and Cedars., 2023). Generally, through consultations and sonographies, doctors can identify a patient's lack of or irregular ovulation, ovarian morphology, and excess of androgen. Though this assessment has been the leading indicator of PCOS in women globally for decades, studies have shown that the criteria is not entirely accurate in its diagnosis. Its diagnoses are usually misinterpreted or overinterpreted as a de facto diagnostic test, and ignores the possibility of a dominant follicle or a corpus luteum (Smet and McLennan, which produces the hormone progesterone that makes your uterus a healthy environment for a developing fetus ("Corpus Luteum", 2025). The usage of this and other criteria also varies and has caused discrepancies. Along with the Rotterdam criteria, two others exist as well, the AE-PCOS Criteria and NIH Criteria. The AE-PCOS (Androgen-Excess PCOS Society) criteria is a less common criteria used to diagnose PCOS based on whether or not a patient has an excess of the androgen hormone (AE) (Yan et al., 2021). The NIH (National Institutes of Health) Criteria is similar to the Rotterdam Criteria but still not recommended to use for diagnosis as it is based on having the presence of hyperandrogenism as well as oligo-amenorrhea (Yan et al., 2021), the irregularity or absence of menstrual periods ("What…Oligomenorrhea", 2025). In a study done on the diagnosis of PCOS in China, when considering the usage of the Rotterdam, AE-PCOS, and NIH Criteria, only 31.3% of OB/GYN's, and other physicians actually used these criteria in their PCOS diagnoses (Yan et al., 2021). These criteria do not always allow for thorough diagnoses. Specifically with the 2003 Rotterdam Criteria, over 30-50% of patients with normal ovulation and levels of androgen could be diagnosed with PCOS (Christ and Cedars, 2023). Due to these and other possible factors existing besides PCOS, the extent of the Rotterdam, AE-PCOS, and NIH Criteria's accuracy is likely lower than expected.

Current and Future Therapeutics

Some therapeutics available are Oral Contraceptive Pills (OCPs), Dietary Therapy, Assisted Reproductive Technology (ART), and Laparoscopic Ovarian Drilling (LOD) (Khan et al., 2019). The OCP's target more specific areas, as they regulate many endocrine irregularities including hirsutism, excess hair growth on the body, and acne. Because of the lowered risk of endometrial cancer through these pills, they are seen as a better option to other therapies (Khan et al., 2019). However, across ethnicities, according to a study, there was no difference found in the level of hirsutism between patients on the OCP's and patients who were not, and they are also associated with hyperglycemia and higher insulin resistance (Khan et al., 2019), indicating a need for these drugs to be further developed, especially for ethnicities which already have a larger susceptibility for insulin resistance, such as South Asian and Hispanic patients. Assisted Reproductive Technology (ART) is the most commonly utilized therapy treatment for PCOS, through stimulating the ovaries and formulating multiple follicles (Khan et al, 2019). However, this form of therapy has been known to cause ovarian hyperstimulation syndrome (OHSS), which

can cause ovaries that are overstimulated to increase and release chemicals into the bloodstream ("Ovarian Hyperstimulation Syndrome", 2025). Because obesity has been reported in at least 50% of PCOS patients (Hoeger, 2020), many symptoms, including insulin resistance, annulations, and irregular menstrual cycle are thought to be reduced through dietary therapy (Khan et al., 2019). However, these dietary therapies have not had significant results. LOD's are used in order to allow for a patient's proper ovulation, which in effect can improve the production of ovarian androgen and decrease insulin resistance (Sinha et al., 2019). It is important to note that LOD's are still a relatively recently developed therapy, and that its full implications and effects have not been thoroughly researched as of date.

Though all forms of diagnostics and therapies have had success, similar to LOD's, these diagnostic criteria and therapies have not had enough extensive research done to fully understand their effects. Furthermore, despite these diagnostic criteria being in place for over two decades, About 75% of patients with PCOS are unidentified in clinical practice (within the United States alone) (Christ and Cedars, 2023). Because multiple phenotypes of the disorder exist, utilizing such broad criteria for diagnosis leads to therapies and treatments that exist only at a surface level. It is evident that in order to and mend these diagnostics and therapies, it is necessary for further research on these and other potential variations of them for a decrease in complications. Through honing in on specific, and common comorbidities within patients with PCOS, new therapies and potential medicines can be created not just to improve treatment accuracy as a whole but also to provide specific therapies to patients based on determining factors of PCOS comorbidities, especially in relation to ethnicity.

Conclusion

There are multiple genes that when mutated, dysregulate hormones in a woman's body that result in PCOS, various comorbidities, and medical conditions. However, the commorbidities that are present and how they manifest can depend on multiple factors, one of which is ethnicity. This highlights the need for current treatment and diagnosis methods to account for these ethnic specific differences. Though it has been researched at a larger scale for the last 50 years, PCOS still remains an endocrine disorder that needs more extensive research in order to develop proper treatments and diagnosis for women of different minorities.

Genetic mutations in PCOS are mainly caused by specific polymorphisms, which change the gene expression and function. These polymorphisms mainly affect genes regulating specific hormones and the mitochondria, both of which are vital for modulating the endocrine system in the body. The mitochondria specifically is a common target for polymorphisms that leads to mitochondrial dysfunction, a type of comorbidity associated with PCOS. Different polymorphisms result in a variety of medical issues and comorbidities, leading to four common phenotypes of PCOS. These phenotypes are labeled by A,B, C, and D, and are differentiated by the presence of numerous polycystic ovaries, oligoanovulation, and/or hyperandrogenism.

Depending on a patient's ethnicity, PCOS results in multiple combinations of comorbidities/medical issues. Certain polymorphisms, alleles, and hormonal mutations are associated with specific ethnicities such as the CY17A1 gene in North Indian women or the rs12970134 and rs17782313 alleles in Saudi Arabian women. Thus, these polymorphisms relate to the presence or absence and variations of comorbidities/medical conditions as a result of PCOS. For example, rs17782313, can cause those with PCOS to experience obesity, as observed in Saudi

Arabian women. Other common commorbidities associated with ethnicity, polymorphisms, and PCOS include infertility and metabolic syndrome.

The main method of diagnosing PCOS is through the Rotterdam criteria, which is based on at least two of three certain characteristics being present to be diagnosed: hyperandrogenemia and/or hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology. However, this criteria does not account for other possible factors, such as teenage patients having extra visible follicles on an ovary, therefore diagnosing them with PCOS can be misleading. There are multiple exceptions to this criteria, and despite being the leading method, is still undergoing development to more accurately diagnose PCOS in women. Apart from the Rotterdam criteria, the NIH and AE-PCOS criteria are also used for diagnostic purposes. Different therapies, such as oral contraceptives and dietary therapy are also utilized to help treat PCOS as well. Note that similar to the Rotterdam criteria, these diagnostic criteria and therapies are still being researched, and can still vary based on a patient's ethnicity.

It is important to understand and visualize the underdevelopment of PCOS research in general, but especially in minorities. Women's health issues have been generationally overlooked, and because Poly-Cystic Ovary Syndrome is a fairly recently discovered endocrine disorder, its extent of research has to be diversified and expanded to create and disperse medicines and therapies to women of all ethnicities, pertaining to their specific comorbidities that can occur from PCOS. Ideally, through prioritizing research of medical diagnosis issues and comorbidities occurring through PCOS, researchers can create new gateways for specialized therapies, especially to minorities, ultimately minimizing the discrimination that exists even today in the medical industry.

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A Review of Emerging Therapeutic Strategies for Alzheimer's Disease: Intranasal Administration of Neuroprotective Agents

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Abstract

cognitive decline, neuronal loss, mood disorder, and hallmark pathologies such as β-amyloid plaques and neurofibrillary tangles. Current treatments, primarily taken orally, provide only modest relief for symptoms and are associated with several adverse effects, highlighting the need for new therapeutic approaches. Intranasal drug delivery bypasses the blood-brain barrier, offering direct access to the brain with higher bioavailability and fewer systemic side effects. This review examines the efficacy of three intranasal therapies, insulin, rivastigmine, and anti-amyloid-β monoclonal antibodies. Evidence shows that intranasal insulin supports cognition, prevents neuroinflammation, and stabilizes biomarkers in both animal models and clinical trials. Intranasal rivastigmine has been shown to enhance olfactory deposition, bioavailability, and cognition, and has also demonstrated some neuroprotective effects, although human evidence remains limited. Anti-amyloid-β monoclonal antibodies have demonstrated increased antibody presence in the brain, reduced amyloid-β plaque burden, and improvements in behavioral function within animal models, although it also is awaiting further clinical testing. Taken together, current findings suggest that intranasal therapies are a promising frontier for Alzheimer's treatment, given that pre-clinical studies demonstrate their improved efficiency and efficacy over similar oral treatments. Intranasal insulin is the most strongly supported of the three, showing promise in clinical trials by slowing cognitive decline and supporting neuronal health within individuals living with AD. Future progress will require large-scale clinical trials, delivery optimization, and formulation strategies to confirm whether these therapies can meaningfully modify disease progression in the clinical setting.

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A Review of Emerging Therapeutic Strategies for Alzheimer's Disease: Intranasal Administration of Neuroprotective Agents

Introduction

Alzheimer's disease (AD) is the most common cause of dementia worldwide and it's currently one of the most pressing challenges in modern medicine. AD currently affects 7.2 million adults in the US and 55 million adults in the world (Bright Focus 2025). AD is a progressive neurodegenerative disorder, characterized by neuronal loss, mood disorder, cognitive decline, functional impairment (McKhann et al., 2011). Cognitive decline in AD often begins as subtle memory lapses and advances towards profound impairments in daily functioning (ig. planning and problem solving), reasoning, and language (Weintraub et al., 2012). Neuronal loss is driven by synaptic dysfunction and neurodegeneration, as a result of the buildup of beta-amyloid plaques and neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein. Together, these pathological

hallmarks lead to widespread cortical and hippocampal atrophy. Current treatments, including oral rivastigmine and acetylcholinesterase inhibitors, provide only modest symptomatic relief, experience poor bioavailability, and are unable to stop or reverse neurodegeneration, demonstrating the immediate need for novel therapies that target disease progression (Alzheimer's Association, 2024). One promising strategy that is currently undergoing research is the intranasal administration of neuroprotective agents, which aims to improve outcomes in AD by targeting both cognitive decline and neuronal loss. Unlike oral or intravenous drugs, which must first undergo metabolism and face challenges in reaching the brain, intranasal (IN) delivery can bypass the blood-brain-barrier (BBB). Drugs delivered intranasally travel along the olfactory

3 epithelium and trigeminal pathways, which enter the central nervous system (CNS) directly through extracellular and intracellular transport (Fonseca et al., 2021). This mechanism enables higher concentrations of the pharmaceutical compound to reach the brain at a faster rate, while also reducing adverse effects. One example, intranasal insulin, has been shown to modulate memory and energy metabolism without causing the hypoglycemia associated with intravenous insulin. Furthermore, intranasal rivastigmine has demonstrated improved brain targeting compared to oral delivery (Freiherr et al., 2013; Guo et al., 2024).

Intranasal delivery is also promising because it is less invasive than intravenous infusions, can be administered repeatedly at home, and has the potential to target specific brain regions associated with memory and executive function. However, nasal sprays face challenges such as uneven absorption, small dosing limits, and possible irritation inside the nose (Chapman et al., 2013). To address these issues, researchers are developing

methods like adding absorption enhancers,

Fig 1. Cranial nerve pathways associated with intranasal delivery. From"https://www.researchgate.net/figure/Schematicdiagram-of-intranasal-drug-delivery-Drugs-in-the-nas al-cavity-bypass-the_fig5_378563641"

using sticky (mucoadhesive) coatings, and designing better spray devices to help the drug stay longer and be absorbed more consistently (Djupesland, 2013). Another challenge is drug breakdown by nasal enzymes before reaching the brain, but mucoadhesive polymers can help by extending nasal residence time and improving

4 passage across the BBB. Given the global burden of Alzheimer's disease, the limitations of current therapies, and the promise of intranasal delivery, it is important to evaluate how effective intranasal therapies truly are. This paper seeks to evaluate the extent to which intranasal administration of neuroprotective agents slow cognitive decline and prevent neuronal loss in patients diagnosed with Alzheimer's disease. By focusing on leading intranasal candidates, insulin, rivastigmine, and anti-amyloid-beta monoclonal antibodies, this review will assess the strength and current evidence in both human and animal studies of intranasal therapies and their potential as disease-modifying strategies for AD.

Intranasal Insulin

Intranasal insulin is a spray formulation designed to deliver small doses of insulin directly to the brain by way of the nasal passages, bypassing the BBB and limiting systemic exposure (Freiherr et al., 2013). It targets brain insulin signaling and metabolism, processes that support synaptic function and help regulate amyloid and tau pathology, mechanisms thought to be a

significant cause of memory loss and neuronal damage in Alzheimer's disease (Freiherr et al., 2013). Normally, insulin regulates synaptic plasticity, increases neurotransmitter (NT) release, and supports neuronal glucose metabolism. These functions are critical because the brain alone can consume up to 20% of the body's glucose supply, despite its relatively small size (Kováč et al., 2010). When neurons lose access to insulin, they also lose the ability to efficiently use glucose, leading to reduced energy availability, synaptic dysfunction, and eventual cell death. This kind of metabolic disruption is recognized as a contributor to AD progression, often referred to as "type 3 diabetes" (Freiherr et al., 2013). Insulin influences central pathologies of

5 AD, suppressing tau hyperphosphorylation and reducing beta-amyloid aggregation which modulates AB-degrading enzymes, including insulin-degrading enzyme (IDE). Through these mechanisms, intranasal insulin has the potential to restore metabolic homeostatic equilibrium and synaptic function while counteracting amyloid and tau pathology that progress AD. Clinical research shows that intranasal insulin can provide clear benefits for patients with Alzheimer's disease.

Fig. 2: Cognitive activity in response to daily doses of 20IU or 40IU intranasal insulin. From "Craft, S., Baker, L. D., Montine, T. J., Minoshima, S., Watson, G. S., Claxton, A., Arbuckle, M., Callaghan, M., Tsai, E., Plymate, S. R., Green, P. S., Leverenz, J., Cross, D., & Gerton, B. (2012). Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Archives of neurology, 69(1), 29–38. https://doi.org/10.1001/archneurol.2011.233" In a double-blind, randomized, placebo-controlled pilot trial, AD patients who received daily doses of 20 IU or 40 IU of intranasal insulin demonstrated stronger delayed memory and better maintenance of daily functioning compared to those given placebo. Brain imaging with FDG-PET scans, which measure how the brain uses glucose for energy, revealed that insulin-treated groups did not experience the same decline in brain metabolism seen in the

6 placebo group. In addition, cerebrospinal fluid (CSF) biomarkers - proteins in the fluid surrounding the brain and spinal cord that reflect disease activity - moved in healthier directions which improved AB42/tau ratios (Craft et al., 2012). In another randomized study lasting 12 months, researchers found that intranasal insulin shifted CSF immune markers, raising IFN-y and eotaxin while reducing IL-6, and these changes were associated with more stable Alzheimer's biomarkers and improved clinical outcomes compared to placebo. This suggests that insulin therapy not only supports cognition but also helps control inflammation in the brain (Kellar et al., 2022). Supporting evidence from reviews of both animal and early human studies further shows that intranasal insulin consistently improves memory and brain metabolism, though results can vary depending on genetic risk factors such as APOE-E4 (Craft et al., 2012). These reviews also note that long-term use may risk insulin resistance, so future trials must carefully examine dosing and treatment duration (Freiherr et al., 2013). Overall, these results suggest that intranasal insulin is one of the most promising metabolic-based treatments for Alzheimer's disease. By directly contacting the brain, it can restore energy balance, regulate synaptic function, and reduce critical diseases such as amyloid and tau. So far, clinical results suggest that not only will memory and everyday function improve in the short-term, but there will also be significant changes in brain metabolism and immune system activity that may prevent disease progression. If these findings are replicated in larger and longer human studies, intranasal insulin may transition from a supportive therapy to a crucial disease-modifying medication. Future studies should improve methods of administration for dosages to minimize resistance and identify which patients (for example, those

with specific genetic risks like APOE-E4) respond best. Still, the consistency across animal and human studies makes it reasonable to predict that intranasal insulin could become one of the first widely used

7 non-invasive therapies to alter the course of Alzheimer's disease, rather than only treating symptoms.

Intranasal Rivastigmine

A second intranasal therapeutic approach is the delivery of rivastigmine, a cholinesterase

inhibitor widely used as a symptomatic treatment for Alzheimer's disease. Rivastigmine works by inhibiting acetylcholinesterase (AChE) , the enzyme responsible for breaking down acetylcholine in the synaptic cleft. By blocking this re-uptake enzyme, rivastigmine increases acetylcholine, thereby promoting cholinergic neurotransmission, a system critically impaired in AD. The cholinergic hypothesis of AD suggests that the degeneration of basal forebrain cholinergic neurons leads to impairments in attention, learning, and memory. In theory, Rivastigmine can restore some of this function, but when orally or via transdermal patches, its effectiveness is limited by poor penetration across the BBB and systematic side effects, such as gastrointestinal distress, anorexia, and bradycardia. Intranasal delivery of rivastigmine bypasses these barriers by allowing it to directly enter the CNS through the olfactory and trigeminal pathways, enabling higher local concentrations in the brain and reducing peripheral toxicity. Formulation studies have optimized this route by combining rivastigmine with a thickening agent (RC-591) and a permeation enhancer to improve deposition in the olfactory region. Guo et al. (2024) tested these formulations using a 3D-printed nasal cavity model to demonstrate airflow and deposition patterns, confirming that the optimized spray, formulation F2, achieved higher time in the olfactory area compared with standard oral dosing.

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Fig. 3: [CAPTION] From "Guo, H., Wang, G., Zhai, Z., Huang, J., Huang, Z., Zhou, Y., Xia, X., Yao, Z., Huang, Y., Zhao, Z., Wu, C., & Zhang, X. (2024). Rivastigmine nasal spray for the treatment of

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To confirm brain delivery, they used in vivo Sprague-Dawley imaging with fluorescent tracers and chemical analysis of brain tissue, both of which showed stronger drug accumulation in the hippocampus and cortex, regions which are important to memory and learning. Additionally, permeation enhancers like chitosan can open tight junctions in the nasal lining and extend contact time, which allows drugs like rivastigmine to stay longer and be absorbed more effectively (Fonseca et al., 2021). In preclinical animal studies, the optimized intranasal rivastigmine produced functional benefits. In Sprague-Dawley rats, individuals given intranasal rivastigmine performed better on memory-based behavioral tasks such as the Morris water maze, a test of spatial learning, and passive avoidance, a test of memory retention, compared to those

9 given oral formulations (Guo et al., 2024). Biochemical assays also showed that intranasal treatment restored acetylcholine levels in the hippocampus and cortex and protected

basal forebrain cholinergic neurons from further loss. Together, these findings suggest that nasal formulations can improve not only drug delivery and bioavailability but also cognitive performance and neuroprotection. Taken together, intranasal rivastigmine demonstrates how engineering delivery systems to target the olfactory pathway can enhance both drug exposure and clinical benefit while reducing negative effects. However, more human trials are still needed to confirm long-term safety, tolerability, and consistency of dosing. Given these positive preclinical results, it is possible that intranasal rivastigmine, if proven safe and effective in humans, has the potential to replace oral rivastigmine as a new potential therapy for symptomatic relief in Alzheimer's disease, especially because it combines improved brain delivery with reduced systemic damage. There is now increasing research on intranasal delivery of larger, disease-modifying therapies, such as anti-amyloid-β monoclonal antibodies, which directly target one of the core pathological hallmarks of AD.

Intranasal Anti-Amyloid-β Monoclonal Antibodies

A third promising strategy for intranasal therapy in Alzheimer's disease is the delivery of anti-amyloid-β monoclonal antibodies. These antibodies are designed to bind directly to amyloid-β (Aβ) peptides, which clump together to form plaques, a major pathological hallmark of AD. By neutralizing and clearing Aβ, antibody therapies aim to slow or even reverse the buildup of plaques, protect synapses, and improve cognition in following with the amyloid cascade hypothesis, which suggests that Aβ buildup causes tau tangles, synaptic dysfunction, and

10 neurodegeneration. Traditionally, these therapies have been administered intravenously, but this route faces several challenges, including poor penetration across the BBB, instability in the bloodstream, and systemic side effects such as neuroinflammation or metabolic disturbances, such as changes in blood sugar.

Importantly, intravenous antibody administration is also associated with amyloid-related imaging abnormalities (ARIA), including brain swelling (edema) and small brain bleeds (microhemorrhages), which likely result from impaired clearance of Aβ through cerebrospinal fluid pathways. While IV treatment has shown modest cognitive gains of only a few points on the CDR-SB, this benefit comes at the expense of serious ARIA risk. In contrast,

Fig. 4: Mechanism of action of monoclonal antibodies against amyloid-β. From "Mechanism of action of monoclonal antibodies against amyloid-β. Neurotorium. (2025, July 10)."

intranasal delivery reduces systemic exposure and may lower the likelihood of ARIA, making it a potentially safer option for patients who seek cognitive benefits without the associated risk. Intranasal administration offers a potential solution, as it allows antibodies to bypass the BBB through the olfactory and trigeminal pathways, delivering them directly to the brain while minimizing potential negative side effects and exposure to the rest of the body. Preclinical research provides strong evidence that intranasal antibodies can reduce amyloid burden and improve functional outcomes. In a study by Cattepoel et al. (2011),

11 APP/PS1 transgenic mice received chronic intranasal administration of a single-chain antibody fragment (22C4 scFv). Using histological staining and biochemical assays, the researchers found a significant reduction in amyloid plaque numbers and amyloid-positive blood vessels, along with redistribution of Aβ from insoluble deposits into more soluble, less toxic forms. The antibody also prevented Aβ from forming fibrils, toxic clumps, and reduced the cell damage

normally caused by Aβ in lab tests, showing that it both protects neurons and helps clear harmful buildup. A later comparative study by Kamei et al. (2022) examined intranasal versus intravenous delivery of an anti-Aβ antibody in App-KI mice. Methods included behavioral memory tests, ELISA assays to measure Aβ levels, and the use of a cell-penetrating peptide (L-penetratin) to enhance nasal uptake. Results showed that intranasal dosing increased antibody concentrations in the brain without raising blood levels, and treated older mice displayed better performance in memory tasks such as maze navigation and avoidance learning. By contrast, intravenous dosing reduced inflammation but achieved weaker brain targeting. Reviews of intranasal drug delivery mechanisms add further support, highlighting how permeation enhancers like chitosan, which opens tight junctions and increases retention, and cyclodextrins, which improve solubility and stability, can boost antibody delivery through the nasal route, though they may also pose risks of local irritation or toxicity (Fonseca et al., 2021).. Together, these findings suggest that intranasal antibodies not only overcome the delivery barriers faced by intravenous administration but also show clear benefits in reducing amyloid pathology and improving cognition in animal models. If these preclinical findings translate reliably into humans, future clinical trials using intranasal antibodies should show not just possible bigger reductions in amyloid plaques, but also significant improvements in cognition and daily life. As larger molecules like antibodies move into intranasal therapeutic pipelines,

12 they represent a crucial next step in testing whether nose-to-brain delivery can provide disease-modifying treatments for AD.

Discussion

Alzheimer’s disease (AD) remains one of the most devastating neurodegenerative

disorders, affecting millions worldwide and marked by relentless cognitive decline, neuronal loss, and mood disorders. While current treatments, such as oral rivastigmine, provide only modest symptomatic relief, intranasal therapies represent a promising new frontier by bypassing the blood-brain barrier and delivering drugs directly to affected brain regions. This review has explored three major approaches: intranasal insulin, rivastigmine, and anti-amyloid-β monoclonal antibodies, to assess the extent to which they slow cognitive decline and prevent neuronal loss in patients living with AD.

The evidence reviewed suggests that intranasal insulin has the most advanced clinical

support, with multiple trials demonstrating improvements in memory, daily functioning, and biomarker stability, alongside neuroprotective effects observed in animal models. Intranasal rivastigmine has shown strong promise in preclinical studies, improving drug bioavailability and deposition in the olfactory region and also enhancing cognitive performance in animal models. Intranasal anti-amyloid-β monoclonal antibodies have also demonstrated positive pre-clinical

results, including reductions in plaque burden, improvements in synaptic health, and improved

cognitive performance in animal models; however, human trials are still necessary to confirm these benefits.

If the evidence from both preclinical and early clinical studies is correct, intranasal

therapies could become an important complement to existing Alzheimer's treatment. Their

13 advantages, including greater brain bioavailability, fewer systemic side effects, and the potential for repeated, efficient, and non-invasive administration, make them uniquely suited for long-term disease management. Looking forward, the success of this strategy will depend on the optimization of delivery, such as the refinement of permeation enhancer formulations. Additionally, consideration should be given to the design of large-scale clinical trials capable of evaluating not only biomarker change but also meaningful preservation of cognition, daily function, and quality-of-life in individuals living with AD.

In conclusion, intranasal administration of neuroprotective agents offers a biologically

plausible and technologically feasible pathway to slow the progression of Alzheimer's disease. While much work remains before these treatments can become widespread, the existing evidence in pre-clinical and early clinical studies shows promise that intranasal therapies may become crucial for shifting the therapeutic trajectory of AD and promoting sustained function and improved quality-of-life. To reach their potential, continued investment in translational research, clinical trial enrollment, and delivery innovation will be essential, ensuring that these promising laboratory findings can be transformed into real-world treatments for the millions of individuals and families affected by Alzheimer's disease.

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The Correlation Between Synesthesia and Creativity: A Literature Review

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Abstract

Creativity is most commonly defined as the ability to form innovative associations. A key factor in human cognitive development, creativity is usually involved in multiple daily tasks such as solving problems in the best possible way or coming up with novel solutions. It is the ability that scientists use to figure out scientific questions, and the tool that artists use to create their masterpieces. As the driving force of human development and innovation, creativity has led to millions of great inventions in human history such as the first microscope and Artificial Intelligence technology, and it has led to the birth of famous artistic works such as "The Starry Night" by Vincent Vangogh.

Creativity is a complex process that relates to both cognition and emotion (Gu et al., 2018). Multiple brain regions work collectively for creativity to function (Sawyer, 2011). The brain also works consciously and unconsciously to form creativity. The default mode network (DMN), a network that is activated during mind-wandering and internal processing, is responsible for the unconscious processing of creativity. In addition, neural plasticity during training can alter the brain regions activated during the creativity process, with different types of creation-related arts having different changes in stimulation (Berkowitz, 2010). Altogether, creativity is a complex process that needs to be better understood.

Some people, surprisingly, show a much higher level of creativity than the normal baseline through an interesting phenomenon. Synesthesia is a phenomenon in which people experience multiple senses when conducting a task that usually evokes only one sense. People with synesthesia experience the unusual activation of another unstimulated sense when a certain sense is being stimulated (Neckar & Bob, 2014). For example, people with grapheme-color synesthesia can see colors in numbers or words; people with chromesthesia experience colors in sounds; people with auditory-tactile experience physical sensations in sounds. These special images are immediate and spontaneous, suggesting that they are not formed deliberately to build the connection between the stimulus and the response. The pairing between the stimulus and that specific response is consistent, suggesting that they would not change with time (Domino, 1989).

Synesthesia itself has some novel functions that may have influenced the creation of many art works. For example, some scholars think that C. Debussy experienced synesthesia based on his work "The Lullaby of the Elephant Calf" (Galeyev, 2007). Several studies investigating the correlation between synesthesia and creativity level have demonstrated that people with synesthesia have a significantly higher level of creativity than other people through different dimensions of measures, especially the level of artistic creativity (Domino, 1989; Ward et al., 2008). However, the underlying mechanisms of this connection are still under discussion. Hence, this paper will review how synesthesia shapes people's artistic creativity. Specifically, it will discuss how creativity and synesthesia forms and functions respectively, as well as the connections in mechanisms between the two.

Mechanisms of Synesthesia

Several mechanisms of synesthesia have been discussed by previous researchers. One of the most critical ideas for the formation of synesthesia is the existence of abnormal cross-sensory neural pathways (Neckar & Bob, 2014). Cross-sensory neural pathways are networks that connect distinct sensory cortices and support the associations between different sensory information (Ramachandran & Hubbard, 2001). Brain regions that are not typically strongly associated are linked together in people with synesthesia. For example, people with grapheme-color synesthesia have excessive connections between the visual word form area (VWFA) that processes shapes of letters and numbers and the fusiform gyrus, which encodes colors (Ramachandran & Hubbard, 2001). This type of connection stimulates the perception of color through looking at letters. Usually, these two regions have weak connections, and thus this kind of communication is considered abnormal. Besides this, other regions of the brain are also found to have critical roles in the formation of abnormal cross-sensory connections. V4/V8 in occipitotemporal areas and some other regions in the parietal lobes also have an impact on this relationship. Hubbard and colleagues verified the cross-activation between VWFA and V4 (the color processing area) in their experiment (Ramachandran & Hubbard, 2001). In this experiment, synesthetes and non-synesthetes participants looked at graphemes, letters or numbers, and non-graphemes and underwent functional magnetic resonance imaging (fMRI). The synesthetes group showed significantly higher activation in the V4 region when looking at graphemes than the control group, which indicates their stronger correlation to other visual information when only a letter or number is being shown.

Three main factors contribute to the development of abnormal cross-sensory pathways. The first factor is abnormal synaptic pruning. Synaptic pruning is the process of getting rid of excessive synaptic connections that are not frequently used to increase the efficiency of other more important pathways and functions. However, this trimming balance is disrupted in people with synesthesia, resulting in an excess of neural connections (Tomson et al., 2013). Normally, these synaptic connections are cut down during prenatal development, but people with synesthesia do not undergo this pruning, leading to excessive cross-sensory signaling (Spector & Maurer, 2009). According to Rouw and colleagues, diffusion tensor imaging (DTI) revealed that people with grapheme-color synesthesia have more white matter connectivity between VWFA and V4 (Rouw & Scholte, 2007).

The second factor is the unbalanced neural inhibition pathway. Neural inhibition is the process of suppressing neural activity and thus the firing and communication between neurons. The process works through releasing inhibitory neurotransmitters that bind to postsynaptic neurons and decreases the probability of neurons firing. Here the decreased neural inhibition fails to prevent the unnecessary connections between different sensory regions, which leads to the overactivation of cross-sensory pathways (Neckar & Bob, 2014).

The reduced neural inhibition causes disinhibited feedback loops to occur. Disinhibited feedback loops occur when inhibition of signals is out of order, and signals can, thus, travel backwards from higher-level brain regions to lower-level ones. For example, the higher shape and meaning processing regions send signals back to those lower sensory regions in an uncontrolled manner, which increases cross-sensory perceptions.

Local cross activation is also a factor that increases the chances of synesthesia (Spence, 2011). Local cross activation refers to the direct communication between sensory cortexes that are near each other. Previous studies have shown that the overactivation of parietal lobes that usually

integrate sensory information is being overstimulated and this leads to the hyper binding between different sensory information. For example, people with number-form synesthesia perceive spatial information through numbers, and the parietal lobe plays a key role in strengthening the binding of spatial information and numerical information (Neckar & Bob, 2014). Thus, local cross activation between different regions caused by areas such as the parietal lobe enhanced the bond between unrelated systems.

The right hemisphere might also play a key role in synesthesia because it plays a stronger role in the interconnections between different brain regions than the left hemisphere. It helps to integrate sensory information between different brain regions and form associations. PET results help to prove this by demonstrating increased activation of the right hemisphere when cross-sensory information is being processed (Hubbard et al., 2011). This might be the reason why people with synesthesia experience rare sensory associations as it strengthens the communications between sensory modalities.

Mechanisms of Creativity

Creativity is a complex cognitive process that involves the interaction between multiple brain regions. Creativity is not a single function that originates from a single brain region in traditional theories, but rather a product of the combination of different regions across the brain. Creativity could be defined as the sudden moment of solving a problem and reconstructing the problem. This phenomenon can also be defined as the divergent thinking and convergent thinking that happens during creative thinking. Divergent thinking is the ability to come up with multiple solutions for a single problem instead of focusing on one single resolution, and it is how people figure out different perspectives and solutions for a math problem. Convergent thinking is the ability to narrow down multiple solutions to a single, best option, and it is how we make a decision from several opinions. Creativity is also defined as the ability to improvise and generate new ideas and works for artists, composers, novelists, and scientists. Creativity is important because it is the tool that pushes people to think and generate new ideas and inventions, which build what we are today and how the world would develop in the future. Increasing the creativity level could help people come up with more innovative ideas which eventually benefit the whole human society and productivity. Thus, understanding the mechanisms underlying creativity is critical for boosting creativity in an effective way.

Creativity has several mechanisms. First, distant semantic information must be associated for creativity to happen. Semantic information are the concepts that are weakly-correlated or unrelated in normal situations. Semantic information expresses meanings for comprehension and deep processing. The right anterior superior temporal gyrus (RH aSTG) increases in activity when creative solutions are being made when solving remote associates tests, and this connects distant semantic concepts together (Seger et al., 2000).

Second, some brain areas may help people to avoid having a fixed thinking mindset which, in other words, will create new solutions for problems that deviate from traditional schemas. Cognitive fixation occurs when people stick to their set mindset and avoid coming up with new and alternative ideas and are predisposed to a certain way of thinking. The anterior cingulate cortex (ACC) could manage conflicting opinions, which makes people question their current ideas and use critical thinking to think about new ways (Luo & Knoblich, 2007). The left dorsal lateral prefrontal cortex (DLPFC) creates flexibility for coming up with different solutions to a problem

and allows changing between them (Goel & Vartanian, 2005). These all work together to create a better environment for new thoughts to be invented through creativity.

The default mode network (DMN) creates a key period of unconscious mind wandering that is a critical factor for creative insights (Christoff et al., 2009). The DMN is a neural network that is active when unfocused, wandering inner thoughts are formed as well as at rest (Menon, 2023). This mind-wandering period that people have everyday diverts people's focus from daily work to a more relaxed and unconscious state. Insights are usually created when we are in a relaxed state and the DMN is responsible for this state (Mason et al., 2007). People become less focused on their previous solution and are able to broaden their mind and come up with solutions that they never thought about before. Through the use of electroencephalogram (EEG), researchers found that people with higher levels of creativity have this specific resting brain wave pattern of DMN that could probably boost their creativity (Martindale & Mines, 1975).

Studies have shown that creativity is not only mediated by the right hemisphere, which has been the more general consensus for some time. Instead, creativity is mediated by a collaboration between both hemispheres (Carlsson et al., 1999). It is shown that those with higher creativity have stronger and more obvious bilateral coordination than those with lower creativity and have stronger activation on one of the hemispheres.

Another factor contributing to creativity is neural plasticity, which can enhance the activity of certain brain regions involved in creativity. Neural plasticity is the ability of neurons to form new synapses, priming existing and useless connections, or strengthening important neural connections. Different extents of musical training can lead to distinct effects on various brain regions (Berkowitz, 2010). People with musical training, art training, and dance training have different neural pathway activation patterns than people who have never been trained with these techniques before (Fink et al., 2007). For example, people with art training have a higher delta and alpha band synchronization, which is usually associated with divergent and convergent thinking (Bhattacharya & Petsche, 2005). Thus, training in certain fields could strengthen the pathways of creativity, and the brain regions used to complete the task.

The parietal lobe and its role in creating hyper binding between different sensory regions is also linked to creativity (Sandkühler & Bhattacharya, 2008). The parietal lobe is responsible for integrating different information, including distant semantic concepts ("The Parietal Lobe and Language," 2018). For example, when solving the remote associates test, the parietal lobe works to associate the weak cognitive links between different information. Dancers also experience alpha synchronization in the posterior parietal regions during the improvisation imagery task, which further indicates the important role that the parietal lobe plays in forming novel connections (Fink et al., 2007).

Correlation between synesthesia and creativity

In this section, the relationship between synesthesia and creativity will be discussed. The correlation between synesthesia and creativity is suggested through their concurrence and their overlapping mechanisms.

Co-occurrence of synesthesia and creativity

In Domino's experiment of creativity level in fine arts students with or without synesthesia (Domino, 1989), subjects from synesthesia groups and the control group were tested on their thinking abilities and creativity through questionnaires testing their creativity level. They found

that there is indeed a correlation between synesthesia and creativity, but they found a more significant correlation between frequency of having synesthesia experiences and vividness of synesthesia than their correlation with creativity.

In Ward and colleagues' research (Ward et al., 2008), they studied artistic creativity through the perspective of divergent thinking and convergent thinking. First, a consistency test was used to identify if participants truly have synesthesia or not scientifically. Then, two psychometric tests were taken to measure convergent thinking and divergent thinking respectively. The remote associates test (RAT) was used to measure convergent thinking. The alternative uses task (AUT) was used to assess divergent thinking. The researchers also studied the correlation between time spent on arts and creativity. They found that the time spent on arts depends on their different types of synesthesia they had. People who experienced visual sensations in music spent more time playing music than people with other types of synesthesia. Through the RAT and AUT tests, they also found that creativity in synesthetes is higher than that of control groups, and it is not correlated with the amount of time they devote in arts. Taken together, synesthetes were shown to have higher levels of creativity than non-synesthetes, indicating that synesthesia and creativity are often associated.

Synesthesia and creativity share some overlapping similarities in mechanisms

First, both synesthesia and creativity involve the usage of cross-modal association. Synesthesia involves connecting different senses together. The abnormal connections between previously weakly-linked sensory cortices trigger the stimulation of multiple senses at a time when only one dominant sense is being used for a task (Galeyev, 2007). These connections are similar to the creativity formation process where unrelated conceptual domains are being linked together and creative ideas are formed. Creativity depends on distant connections between semantic or functional brain regions. Hence, both of them depend on the association between different brain regions that do not connect together in normal daily tasks, which creates unusual experiences of senses and novel ideas (Merter, 2017).

Second, both synesthesia and creativity involve hyper binding of information in the parietal lobe. The parietal lobe in synesthetes is hyperactivated (Kadosh et al., 2007), leading to stronger integration between different sensory systems. The parietal lobe also supports the integration of divergent thinking, convergent thinking, and the combination of cross-domain concepts, which is the key part of forming innovative ideas (Sandkühler & Bhattacharya, 2008). Thus, both processes involve having the parietal lobe to integrate a single piece of information into a whole part of the multiple information.

Third, synesthesia and creativity both involve a strong effect from the right hemisphere. For synesthesia, the right hemisphere plays a key role in the cross-modal association as it enhances the connections between different sensory cortices and acts as an important messenger in integrating different senses (Rotenberg, 2013). For creativity, even though it is shown to involve both hemispheres collaborating together in its formation process, the right hemisphere still drives the integration of distant concepts and divergent thinking, which facilitates the conceptual pairing for higher creativity level (Howard-Jones et al., 2005). Thus, both have a strong connection to the right hemisphere that relay and integrate the important information for their formation.

Fourth, neural plasticity enables the formation of both synesthesia and creativity. The abnormal synaptic pruning leads to excessive connections between different senses in people with synesthesia, which makes them experience unusual connections between senses that aren't usually

stimulated simultaneously. Neural plasticity also enables the brain to form new connections due to experience such as training. Training in artistic or other techniques could further boost creativity as the creativity pathways are being strengthened due to neuroplasticity (Sawyer, 2011). Thus, neuroplasticity promotes the development of both synesthesia and creativity.

Conclusion

In this review, we examined the literature to demonstrate an association between synesthesia and creativity. Based on the literature, synesthesia and creativity are likely to be correlated, as they share neural mechanisms that enable the connection between different senses or conceptual information. Both of them go beyond the traditional connections in brains and rely on processes that strengthen different associations between information.

Previous key findings underlying the themes of this paper demonstrate this conclusion. Synesthesia, a phenomenon that occurs when people experience different senses when only one sense is being stimulated, relies on cross-modal associations to form. Abnormal synaptic pruning, unbalanced neural inhibition pathway, disinhibited feedback loops, local cross activation, and the right hemisphere all strengthened the previously weak connections between different sensory cortices, which generate and define synesthesia and highlight the different handling methods of information in people with synesthesia.

Creativity, the cognitive process that generates innovative ideas, involves the association between distant semantic information. ACC and DLPFC help with creating alternative solutions to problems. The DMN diverts people's normal attention and leads them to come up with novel ideas. The collaboration between the two hemispheres integrates and boosts the connections between different information, forming valuable new opinions. Neural plasticity strengthens and shapes the creativity pathways that promote people to think and act creatively. The parietal lobe helps integrate information collected from different semantic fields.

Through overlapping neural mechanisms, this study shows that synesthesia and creativity could possibly link together, with one promoting the other. However, this conclusion has limitations. First, no causal relationship can be inferred from current studies. Most of the studies referred to in this paper are correlational studies, such as using questionnaires and imaging to demonstrate the occurrences of both phenomena together. However, it still remains uncertain whether the shared mechanisms affect and cause both synesthesia and creativity, or if they are just related but not overlapping. Second, individual differences still remain. We are not certain whether the conclusions on synesthesia and creativity in these studies are truly due to the effect of synesthesia itself or other factors due to personal disparity, as the sample sizes of the studies are not very large, and the sample choices are limited.

In the future, studies should be conducted to create a better explanation between the connections of synesthesia and creativity. Studies that affect the shared mechanisms between synesthesia and creativity can be used to check if both are being influenced. More samples can also be used to create a larger sample pool to more accurately test the connections between the two. Block design or other methods should be used to exclude the effects of other factors on creative tasks. Longitudinal studies can also be conducted to check the causal relationship between synesthesia and creativity in response to the changing experiences.

This study is important because it proposes a novel insight on how creativity can be promoted. If the connection between synesthesia and creativity truly exists, people could simulate

the way synesthetes think to enhance their creativity level. For example, by combining scent with music pitches, musicians might have a better understanding of the emotions delivered through music notes and could thus have a higher creative level in composing new scripts. If people could figure out how this works, the overall creativity level would increase.

In conclusion, this study connects synesthesia with creativity and reveals the brain's ability to step out of traditional loops and form new pathways to form novel connections. By understanding the connections between synesthesia and creativity, people will have a better understanding on how both form and how we could utilize this association to boost creativity, a key factor in human cognitive development.

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