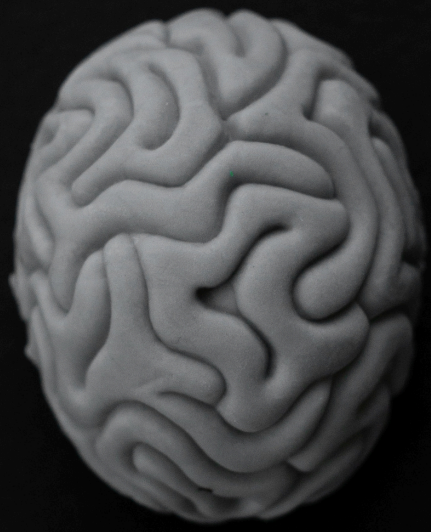
MCMASTER BRAIN
RESEARCH SOCIETY

APRIL 2025 VOLUME FIVE



Cortex

Advancing Knowledge. Shaping Minds.

Acknowledgements

PRESIDENTS

SHUANI WANG
RAENITA PULIYELIL

DIRECTOR OF PUBLICATIONS

HIYA SHAH

DIRECTOR OF EVENTS

CINDY VO

DIRECTOR OF MARKETING

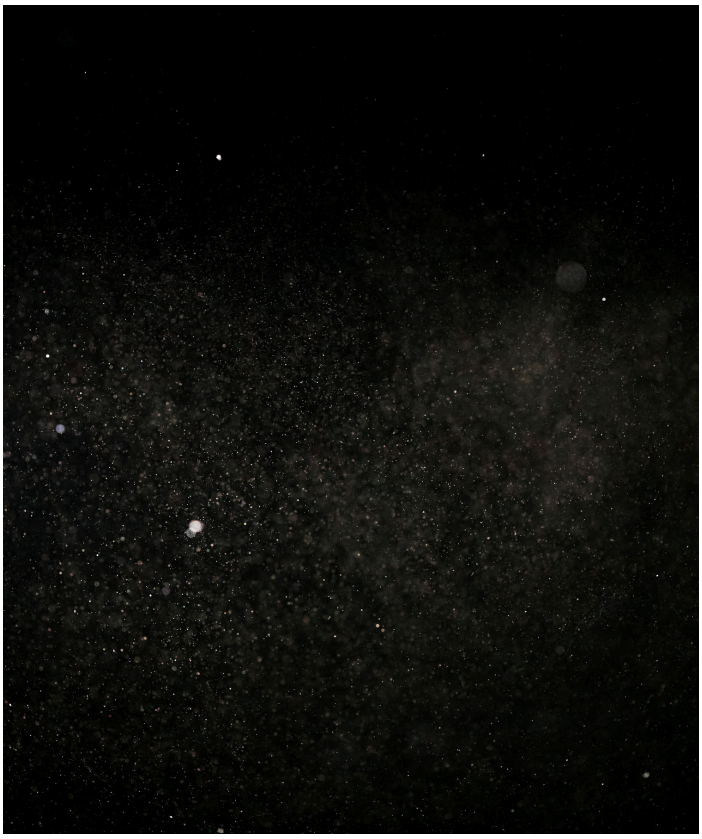
VARSHAA SRIVEL

DIRECTOR OF FINANCE

AHMED MOHAMMED SAEED
ARYAN SOOD

DIRECTOR OF ADMINISTRATION

DALJOT SIDHU



EVENT COORDINATORS

IAN KIM
LAURINE ANDRAWS
MAYA KHALIL

GRAPHIC DESGINER

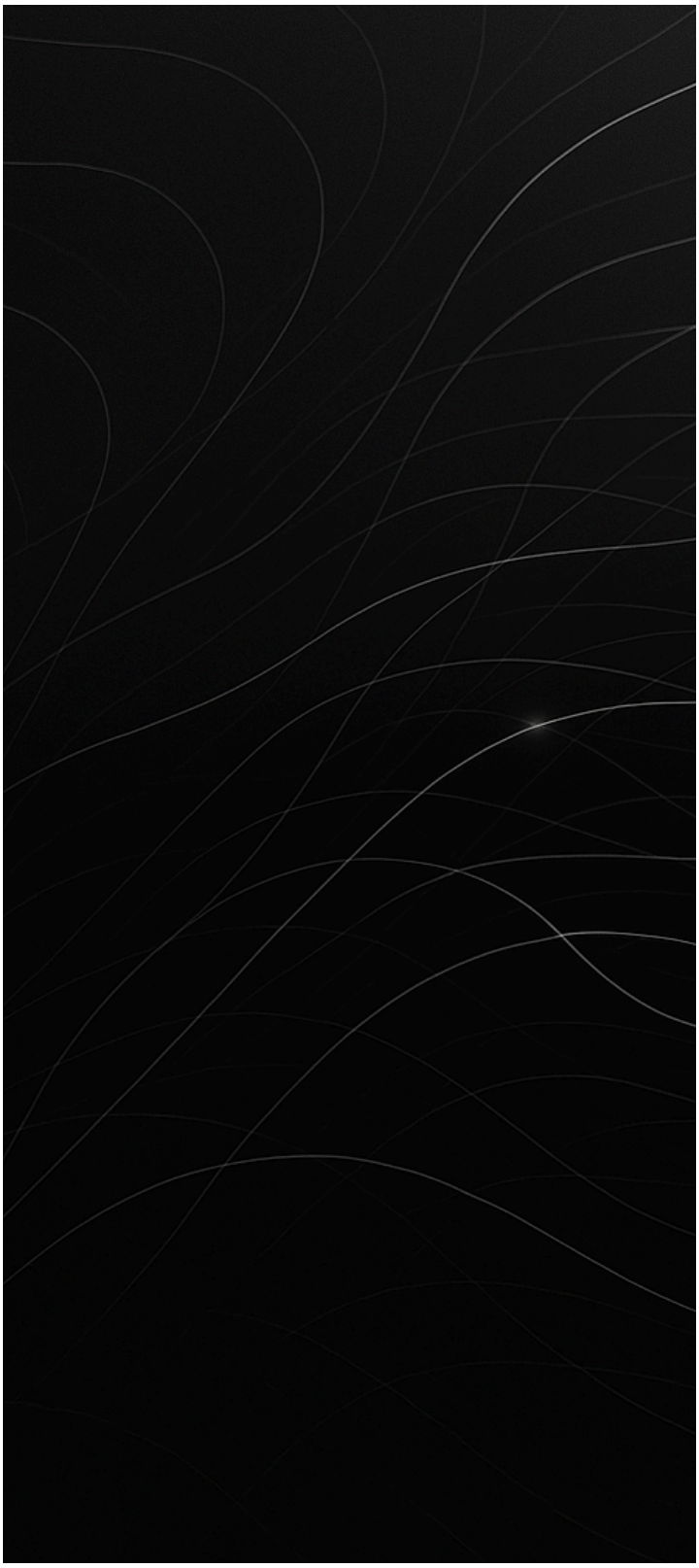
AHMED TALPUR

JOURNAL EDITOR

AUDREY HARUN

McMaster University is located on the traditional territory shared between the Haudenosauneeconfederacy and the Anishinabe nations, which was acknowledged in the Dish with One SpoonWampum belt. That wampum uses the symbolism of a dish to represent the territory, and one spoon torepresent that the people are to share the resources of the land and only take what they need.

TABLE OF CONTENTS



DOCTORS OR ARTIFICIAL INTELLIGENCE?

ASSESSING THE RELIABILITY OF AI IN DIAGNOSING MENTAL DISORDERS

AUDREY HARUN | BACHELOR OF LIFE SCIENCES (HONOURS), *CLASS OF 2027*

VOLUME 5 | 04

Mental illness has long been a delicate subject within the realm of medicine. A careful review and genuine empathy are crucial for understanding a patient's thoughts and feelings, which is essential for providing an accurate diagnosis. Artificial intelligence (AI) has significantly impacted modern healthcare, from improving diagnostic accuracy to enhancing patient care through personalized treatment plans. It has made remarkable strides in healthcare, including early diagnoses, drug development, and medical treatment. Yet, the question remains: can AI be as reliable as a human, and preferred when it comes to diagnosing mental disorders and understanding a human's thoughts, emotions, and overall mental health?

Artificial intelligence (AI) has achieved significant advancements in mental health diagnosis, providing innovative tools that can aid clinicians in identifying and monitoring mental health conditions. For example, AI algorithms have been designed to analyze speech patterns, text inputs, and even facial expressions to detect signs of depression, anxiety, and other mental health disorders. These technologies can process large volumes of data, identifying subtle cues that may be overlooked in traditional assessments. However, despite these advancements, notable challenges remain. A primary concern is the accuracy and reliability of AI in diagnosing mental disorders. Current AI systems often struggle with the complexity and variability inherent in mental health conditions, which can lead to potential misdiagnoses. Data privacy and security issues arise as AI systems require access to sensitive personal information to function effectively. The World Health Organization has also pointed out the uneven application of AI in mental health research, noting that most studies focus primarily on depressive disorders and schizophrenia, leaving other conditions underrepresented (World Health Organization Europe, 2023).

These challenges underscore the need for a cautious approach when integrating AI into mental health diagnostics. It is essential to ensure that technological advancements do not compromise patient safety and well-being. Research indicates a clear preference among patients for human clinicians over AI systems in mental health care (Li, Chen, Liu, & Xu, 2024). Studies have shown that individuals typically adhere less to medical advice offered by AI doctors than human doctors. This preference can be attributed mainly to the unique qualities human clinicians bring to the therapeutic process, such as empathy, understanding, and the capacity to build trust—traits that are notably difficult for AI to emulate. Furthermore, patients often express concerns regarding privacy invasion, and experience diminished satisfaction when engaging with AI systems for mental health assessments. Human clinicians' nuanced care and personalized attention are critical in effective mental health treatment, fostering a therapeutic alliance that AI struggles to establish (Yan, Ruan, & Jiang, 2022). Consequently, while AI can serve as a valuable supplementary tool, the irreplaceable significance of human interaction remains central to patient preferences in mental health care.

Despite AI's advancements in mental health conditions, it cannot replace human clinicians' empathy and trust-building abilities. Mental health care is not merely about analyzing data or recognizing patterns; it involves genuinely listening, reassuring, and meeting patients with empathy and care. A human doctor can perceive more than just symptoms; they remember the emotions, struggles, and unspoken pain that AI cannot fully grasp. While AI can analyze data and recognize patterns, it lacks the emotional intelligence and contextual awareness needed to truly understand the nuances of human experience. The ability to comfort, understand without judgment, and foster genuine connections makes human clinicians irreplaceable. After all, care isn't just about calculations—and even those aren't always perfect, even for AI. While AI can be a helpful tool, true healing comes from feeling seen, heard, and valued—something only another human can genuinely provide.

1. Artificial Intelligence in mental health research: New who study on applications and challenges. (2023). Retrieved from https://www.who.int/europe/news/item/06-02-2023-artificial-intelligence-in-mental-health-research--new-who-study-on-applications-and-challenges
2. Li, S., Chen, M., Liu, P. L., & Xu, J. (2024). Following medical advice of an AI or a human doctor? experimental evidence based on clinician-patient communication pathway model: Health communication: Vol 0, no 0 – get access. Retrieved from https://pubmed.ncbi.nlm.nih.gov/39494686/
3. Riedl, R., Hogeterp, S. A., & Reuter, M. (2024). Do patients prefer a human doctor, artificial intelligence, or a blend, and is this preference dependent on medical discipline? empirical evidence and implications for medical practice. Retrieved from https://pmc.ncbi.nlm.nih.gov/articles/PMC11345249/?utm_source=chatgpt.com
4. Yan, W.-J., Ruan, Q.-N., & Jiang, K. (2022). Challenges for artificial intelligence in recognizing mental disorders. Retrieved from https://pmc.ncbi.nlm.nih.gov/articles/PMC9818923/

THE NEUROBIOLOGY OF MUSICAL EXPECTATIONS: A MECHANISM FOR MUSIC-INDUCED PLEASURE

JEM PAREKH | BACHELOR OF PSYCHOLOGY, NEUROSCIENCE, BEHAVIOUR (HONOURS), *CLASS OF 2027*

The human brain does not passively observe the world but actively predicts what will happen next (1). Individuals apply mental shortcuts, like biases and heuristics, to process incoming stimuli, including implicit predictions about future experiences (1). Implicit predictions help the body to respond to near-future events (2). This mechanism extends to auditory perception, where sound predictions aid in responding to the environment (3). A hierarchy of brain regions supports auditory predictions, including musical expectations (3,4). Musical expectations are predictions about how music will unfold (3,4). The ability to derive pleasure from music suggests an evolutionary adaptation tied to the formation of musical expectations (3). Forming musical expectations allows humans to derive pleasure from music perception.

Carrying out behaviours necessary for survival is rewarded with pleasure (1). The ability to process sound is an evolutionary necessity enabling organisms to detect environmental changes and communicate with others (3).

In humans, auditory processing is critical for speech, allowing for the transmission of ideas and emotional states (3). Such capacities emerge from the interconnectivity of the auditory cortex to other modalities (3).

Auditory perception is hierarchical (3,4). The auditory cortex, located in the temporal lobe, is responsible for processing sound (3). It is structured hierarchically, with core, belt, and parabelt regions that process increasing levels of complexity (3). The core region analyzes basic sound features such as individual pitches, while areas distal to the core process more complex musical elements such as chords, a simultaneous collection of pitches, and melodic contour, the “direction” of a melody through time (3,5). These regions are embedded in a broader neural hierarchy that interacts with higher-order brain areas such as the frontal cortex (3-5). Two pathways have been identified, beginning from the core area of the auditory cortex and traveling dorsally or ventrally toward the frontal cortex (3).

These pathways are bidirectional, forming active feedback loops. Lower-level regions, such as the auditory cortex core, interact with higher-level areas, including the frontal cortices (3,5). Such loops allow the auditory cortex to interact with memory systems (3). This neural hierarchy enables the formation of musical expectations—described by a model known as the predictive coding model of music (PCM) (3,4).

Musical expectations are the brain's predictions of how a piece of music will unfold (3). The PCM proposes that previous experiences and musical memories influence musical expectations (1,4). These memories, known as the musical lexicon, contain information about past musical experiences (4,6). The auditory cortices in the superior temporal gyrus (STG) exhibit increased activity with the nucleus accumbens (NAcc) when forming musical expectations (3). The NAcc is part of the mesolimbic reward system and is involved in making and processing musical expectations (3). The STG's and NAcc's relationship suggests that the STG—where the musical lexicon is housed—influences musical expectations formed by the NAcc (3,6). Essentially, memories from the musical lexicon guide future musical expectations to increase prediction accuracy (6,7). Culture, traditions, and lifetime musical experiences all dictate the collection of memories in the musical lexicon (4). Thus, musical memories stored in the musical lexicon are highly individualized.

Music often evokes pleasure when it offers learning opportunities. The PCM proposes that musical expectations from higher-order brain regions are compared to incoming music stimuli from lower-order brain regions (4). The NAcc processes discrepancies in musical expectations and the incoming music (3,8). Since sound processing is crucial for survival, the brain encourages increased accuracy in auditory predictions with pleasure (8). Pleasure encourages the repetition of behaviours—often those necessary for survival. Therefore, when discrepancies improve the accuracy of future musical expectations, the NAcc—along with the mesolimbic reward system—releases dopamine, evoking pleasure (1-3,8). Musical uncertainty modulates whether the NAcc evokes pleasure (9). It is the degree to which a listener is unsure of an upcoming musical experience (9). For example, musical uncertainty is lowest when the listener's expectations consistently align with the music (9).

Music that challenges a listener's expectations is often pleasurable when musical uncertainty is low (9). Low musical uncertainty indicates that the listener is confident in their expectations. As a result, music that does not align with expectations is surprising, indicating that their expectations were not calibrated to the music (1,3,9). Such conditions allow for learning—individuals can alter their future musical expectations (9).

Learning to improve musical expectation accuracy is pleasurable, providing a positive listening experience. When musical uncertainty is high, music that aligns with a listener's musical expectations is often pleasurable (9). The listener is rewarded when they make the correct prediction in an unconfident context, further refining prediction accuracy (9).

In both cases, the NAcc, with the mesolimbic reward system, releases dopamine to evoke pleasure (3). Finally, the discrepancy signal is sent back up the hierarchy to the musical lexicon as a memory to refine future expectations (1-3). Therefore, implicit learning to improve musical expectation accuracy is rewarded with pleasure.

Forming accurate predictions is crucial for survival (1). Learning to form accurate predictions is adaptive; such behaviour is pleasurable (1,3). Sound, and by extension, music perception, benefit from accurate predictions (1,3,4). Musical expectations are possible because of interactions between higher- and lower-order brain regions (3). These hierarchical interactions integrate past experiences and memories into future expectations (3). Musical expectations differ from person to person because individuals have unique musical experiences (3,4). If musical expectations vary, then pleasure will vary. Thus, these adaptive functions can likely explain the subjectivity of music and individualized music taste/preference. Individuals have different musical tastes due to their differences in generating musical expectations.

Musical uncertainty as a reward factor raises critical questions about how the brain processes familiarity and repetition. Familiar music has been shown to induce anticipation of climaxes (maximal emotional responses) while activating reward systems (3). However, repeated exposure to a piece may reduce musical uncertainty (9). What remains unclear is how the balance between anticipation and learning affects the long-term reward value of music. Future research should investigate how familiarity influences musical expectation processing over time—does a well-learned song continue to evoke pleasure through anticipation, or does familiarity diminish its reward value?

Beyond music, investigating the neurobiology of music-induced pleasure may offer insights into broader aesthetic cognition. Music cognition illustrates how the brain assigns rewards to inconsequential stimuli, a principle that may extend to other art forms such as visual art and literature (3).

Just as novelty in music evokes pleasure, artistic surprises may engage similar prediction-processing mechanisms in other cognitive domains. Exploring these parallels could deepen our understanding of how the brain processes beauty, creativity, and artistic appreciation.

Music cognition integrates auditory processing, memory-based expectations, and reward evaluation through a complex yet ingenious neural network (3,6,7,9). As such, music cognition is an interactive and hierarchical process that requires the collaboration of many neural systems (3,9). Ultimately, the human ability to predict is an instrument that allows abstract sound patterns to be enjoyed as the universal experience that is music.

1. Koelsch S, Vuust P, Friston K. Predictive processes and the peculiar case of music. Trends in Cognitive Sciences [Internet]. 2019 [cited 2025 Mar 3];23:63–77. doi: 10.1016/j.tics.2018.10.006.
2. Barrett LF. The theory of constructed emotion: an active inference account of interoception and categorization. Soc Cogn Affect Neurosci [Internet]. 2016 [cited 2025 Mar 3];nsw154. doi: 10.1093/scan/nsw154.
3. Zatorre RJ, Salimpoor VN. From perception to pleasure: Music and its neural substrates. Proc Natl Acad Sci USA [Internet]. 2013 [cited 2025 Mar 3]110:10430–10437. doi: 10.1073/pnas.1301228110.
4. Cheung VKM, Harrison PMC, Koelsch S, Pearce MT, Friederici AD, Meyer L. Cognitive and sensory expectations independently shape musical expectancy and pleasure. Phil Trans R Soc B [Internet]. 2023 [cited 2025 Mar 3];379:20220420. doi: 10.1098/rstb.2022.0420.
5. Tillmann B, Koelsch S, Escoffier N, Bigand E, Lalitte P, Friederici AD, Von Cramon DY. Cognitive priming in sung and instrumental music: Activation of inferior frontal cortex. NeuroImage [Internet]. 2006 [cited 2025 Mar 3];31:1771–1782. doi: 10.1016/j.neuroimage.2006.02.028.
6. Peretz I, Coltheart M. Modularity of music processing. Nat Neurosci [Internet]. 2003 [cited 2025 Mar 3];6:688–691. doi: 10.1038/nn1083.
7. Pearce MT. Statistical learning and probabilistic prediction in music cognition: mechanisms of stylistic enculturation. Annals of the New York Academy of Sciences [Internet]. 2018 [cited 2025 Mar 3];1423:378–395. doi: 10.1111/nyas.13654.
8. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature [Internet]. 2006 [cited 2025 Mar 3];442:1042–1045. doi: 10.1038/nature05051.
9. Cheung VKM, Harrison PMC, Meyer L, Pearce MT, Haynes J-D, Koelsch S. Uncertainty and surprise jointly predict musical pleasure and amygdala, hippocampus, and auditory cortex activity. Current Biology [Internet]. 2019 [cited 2025 Mar 3];29:4084-4092.e4. doi: 10.1016/j.cub.2019.09.067.

ALZHEIMER'S GUIDE TO GREAT-GRANDMOTHERS

"To my great-grandmother, with love. I wish I got to meet you more"

ACE SANG-YONG KO | BACHELOR OF LIFE SCIENCES, *CLASS OF 2028*

PART I:

As Alzheimer's, it has come to our attention that, in medical journals, there is little attention given to the feelings of the disease itself. As the affected parties: We find this unfair, and terribly rude. The process of memory loss and gradual decay is equally difficult for both parties, and, as we all know: Alzheimer's has feelings too.

So, we open this with a welcome, and lots of hugs. Take these hugs. You will need them.

PART II: An Introduction to Great-Grandmothers (Who are they? Can they hurt me?)

Great-grandmothers, as identified by the Questionable and Dubious World Health Organization (WHO-Q), are parasitic rats living in the attic. Many of our children fear them, as they have the potential to bite. Hard.

The first rule, when dealing with great-grandmothers, is that they often sit in very stark, white rooms. Sometimes, they stare into space. Other times, they smile. When grand-children, or great-grandchildren arrive, great-grandmothers will remember them.

She will smile at them, sometimes, but not other times. There is a fine line between simply not remembering, and not being able to remember.

It is your job to ensure that this line becomes increasingly blurry as time goes on, until even the grandchildren and those around her feel insecure, tired, and melancholy when entering the room. They will cry. You will cry, too. Do plenty of deep breathing exercises while doing so.

PART III: What Can I Do To Support My Mental Health, As A Disease?

She loves you. She loved you. She thought she could love you. The world revolved around her and you weren't even there to see it. There was a time where your father loved her, and you loved the world for it, there was a time where she was alive and well and–

PART IV: Conclusion

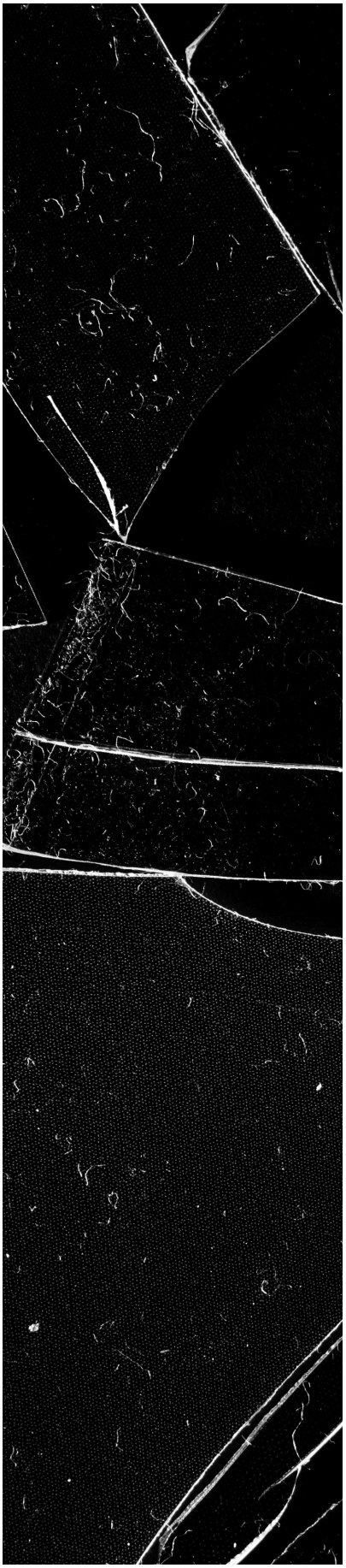
With this, my dear readers–You should be well-equipped to deal with the horrible, and all-encompassing menace known as great-grandmothers.

We wish you all the best in the future–

Three children, two adults, and one woman in a frail bed all gather in a room. The light flickers softly through the curtains. In this moment, she is unbreakable, like some species of moth that drifted aerily into the room. On the way out, one of the children would ask if the family could bring "grand-hamloni" a colouring sheet, since she had so many of them. The child's mother, knowing about our diseases, although the child did not, would shake her head sadly, and say, that it likely didn't matter. But the child won't know why until much later.

This is a sad memory. But there were happy ones, when the child saw the great-grandmother smile, and it was the loveliest thing on the planet. She was just, in that instant, a beacon of joy: A lighthouse, a pillar–

We wish you all the best in the future.



BURNOUT AND NEURAL PLASTICITY: THE LASTING IMPACT OF CHRONIC STRESS ON THE BRAIN

SAHITH RAJKUMAR | BACHELOR OF LIFE SCIENCE, *CLASS OF 2028*
SHYAMILAN PRAGATHESWARAN | BACHELOR OF LIFE SCIENCE, *CLASS OF 2028*

More than 42% of Canadian professionals report feeling burnt out, with Millennials and Gen Z experiencing the highest rates within their groups—up to 55% (Global News, 2024). Burnout is now recognized as a neurobiological disorder involving structural and functional changes, rather than a psychosocial issue - an important distinction that reframes both treatment approaches and societal perceptions. The prefrontal, limbic, and hippocampus circuits are remodelled by prolonged stress and dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity, affecting memory, executive function, and emotional control. Recent data indicates that these stress-induced alterations may be reversible, underscoring the significance of focused therapies to restore brain plasticity.

Neuroplastic alterations related to burnout primarily affect the prefrontal cortex (PFC), which regulates executive function, attention, decision-making, and indirectly impacts the limbic system. Chronic work-related stress triggers dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which has been found to increase cortisol levels. This leads to reduced grey matter in the dorsolateral PFC, disrupting synaptic plasticity (Liston et al., 2009). The abnormalities reduce the ability to regulate emotions and thoughts by weakening the top-down regulatory control over crucial subcortical limbic areas. Functional neuroimaging research has found burnout to be associated with weakened connectivity between the PFC and amygdala, which is linked to cognitive processing and poor stress adaptation (van der Linden et al., 2021).

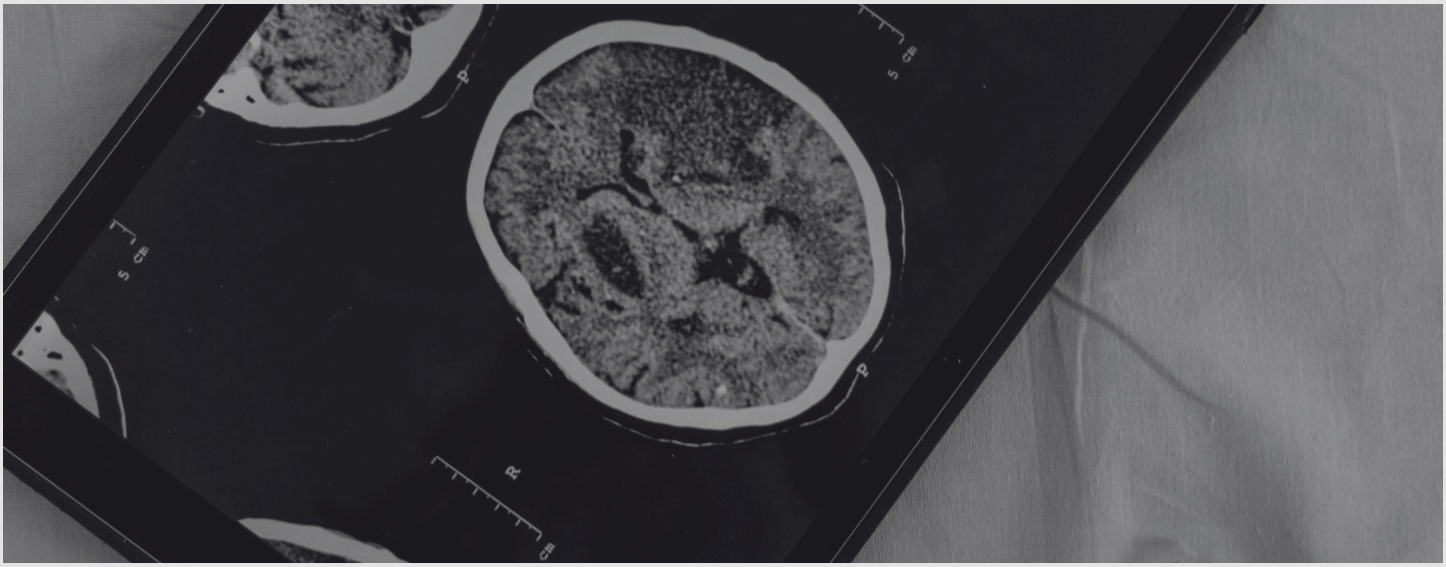
Furthermore, the medial PFC regulates how stress is processed in the amygdala. The medial PFC sends inhibitory signals through GABAergic neural pathways to the amygdala, helping reduce how stress is perceived and preventing the excessive release of stress hormones like cortisol, epinephrine, and norepinephrine (McEwen, 2013). However, when these inhibitory signals are disrupted by excitotoxicity - neuron damage caused by excessive stimulation - and broader neurotoxic effects of chronic glutamate exposure, the amygdala becomes hyperactive and less capable of managing stress (García-Cabrerizo, 2022).

The neurotoxic damage from excess glutamate also compromises working memory and attention, though certain interventions - like mindfulness, therapy, or neuroplasticity-focused treatments - may help mitigate this damage. In addition, the neural disruption perpetuates this decrease in cognitive function and ability to respond to stress by causing dendritic arborization in the amygdala, making it even more sensitive to stress.

BURNOUT'S IMPACT ON THE BRAIN IS ROOTED IN STRUCTURAL DETERIORATION, LEADING TO EXECUTIVE DYSFUNCTION AND IMPAIRED STRESS REGULATION .

Interestingly though, while dendrite arborization worsens the symptoms of burnout, it can also be used as a tool in recovery by increasing the brain's capacity for neural plasticity. The extra synapse s allow for the rewiring of more neural circuits to perform the function of disrupted pathways, such as the GABAergic pathway, allowing the amygdala to recover from stress-induced neural damage . However, it is vital to advocate for new policies to reduce the hours and demands placed on students and employees - measures that are essential to support neural recovery and enhance long-term brain plasticity. Without systemic change, burnout will likely result in a surge of patients with lasting neurological damage - an outcome that could be prevented through policies supporting recovery and reducing chronic stress exposure .

1. Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. Nature Reviews Neuroscience, 10(6), 410–422. https://doi.org/10.1038/nrn2648
2. Davidson, R. J., & McEwen, B. S. (2012). Social influences on neuroplasticity: Stress and interventions to promote well-being. Nature Neuroscience, 15(5), 689–695. https://doi.org/10.1038/nn.3093
3. García-Cabrerizo, R., García-Fernández, J., Burgueño, M., & Manzanares, J. (2022). Alterations in the hippocampal glutamatergic system in a rat model of stress-induced depression: Reversal by fluoxetine. Frontiers in Pharmacology, 13, 944796. https://doi.org/10.3389/fphar.2022.944796
4. Global News. (2024, February). Why studies show burnout is getting worse: 'Employees are exhausted'. Global News. Retrieved from https://globalnews.ca/news/9915532/burnout-canada-workplace-mental-health/
5. Liston, C., McEwen, B. S., & Casey, B. J. (2009). Stress-induced alterations in prefrontal cortical dendritic structure and behavior. Nature Neuroscience, 12(3), 312–321. https://doi.org/10.1038/nn.2261
6. McEwen, B. S., & Morrison, J. H. (2013). The brain on stress: Vulnerability and plasticity of the prefrontal cortex over the life course. Neuron, 79(1), 16–29. https://doi.org/10.1016/j.neuron.2013.06.028
7. van der Linden, D., Keijsers, G. P. J., Eling, P., & van Schaijk, R. (2021). Burnout and brain function: Neuroimaging findings and their relevance for organizational research. Brain, Behavior, & Immunity – Health, 18, 100383. https://doi.org/10.1016/j.bbih.2021.100383



DCAS9-MGMT METHYLATION AND NANOTECH TARGETING OF EGFR AND TERT MUTATIONS FOR GLIOBLASTOMA TREATMENT

ROBIN KOMARNISKI | BACHELORS OF COGNITIVE SCIENCE OF LANGUAGE (HONOURS), *CLASS OF 2025*

Glioblastoma is an aggressive grade IV cancer that rapidly spreads and grows within the brain, characterized by factors such as low rates of recovery and high resistance to treatment. The tumor arises from glial cells, and despite numerous advancements in surgery, glioblastoma remains difficult to treat due to its invasive nature and ability to adapt to treatments.

Observed biomarkers such as gain of chromosome 7p, loss of chromosome 10q (5), elevated choline, reduced N-acetylaspartate and the presence of lactate in MRS scans support the diagnosis of glioblastoma. (2). Additionally, the presence of mutations at the TERT promoter region and the EGFR gene make glioblastoma particularly harder to treat. The TERT promoter is responsible for making telomerase, while the EGFR gene is responsible for making epidermal growth factor receptors, both molecules that are responsib le for cell growth and survival. Therefore, a mutation in these regions allows cancer cells to further evade death and continue dividing, leading to enhanced tumor growth (3). Furthermore, an unmethylated MGMT promoter further intensifies tumor growth, as its unmethylated state indicates that MGMT is active. Since MGMT is responsible for repairing damaged guanine nucleotides, its activity reduces the effectiveness of chemotherapy, which works by damaging guanine in cancer cells. These mutations thereby prom ote uncontrolled growth of the tumor as well as hinder treatment strategies such as chemotherapy, making glioblastoma particularly hard to treat (2,3).

We propose an approach integrating dCas9 epigenetic editing with nanoparticle-targeted therapy. dCas9 is a modified version of the Cas9 enzyme (an enzyme used for cutting DNA) that can no longer cut DNA, but is still able to bind to DNA sequences. This therefore allows dCas9 to act as a delivery system for other proteins, attaching them to certain DNA sequences. Additionally, DNMT is an enzyme that adds methyl groups to DNA, which usually silences DNA expression. Putting these two molecules together creates dCas9-DNMT, which is able to reintroduce methylation at the MGMT promoter (7,8), which studies have shown will “demonstrate a significant reduction in MGMT expression, leading to intensified TMZ chemosensitivity” (7). Intensified TMZ chemosensitivity due to methylation will therefore enable the use of standard chemotherapy, as the tumor cells become vulnerable again to alkylating agents.

Simultaneously, siRNAs loaded with silencing molecules can be used to target the tumor's uncontrolled growth. siRNAs (small interfering RNA) are double stranded RNA molecules that bind to mRNA sequences, and through a process called RNA interference, silence the genes that these mRNA sequences code for. siRNAs can therefore be used to silence TERT and EGFR, two mutations present in glioblastoma that make the tumor particularly hard to treat (as mentioned above). Specifically, an anti-hTERT siRNA-loaded nanoparticle (targets the TERT promoter) (6) and a liposome backbone with siRNA-EGFR coating (targets EGFR) (1) can deliver molecules that silence/inhibit the mRNA responsible for coding for TERT and EGFR. This therefore minimizes tumor proliferation due to a decrease in the creation of telomerase and epidermal growth factor receptors, which as a result decrease tumor maintenance and progression.

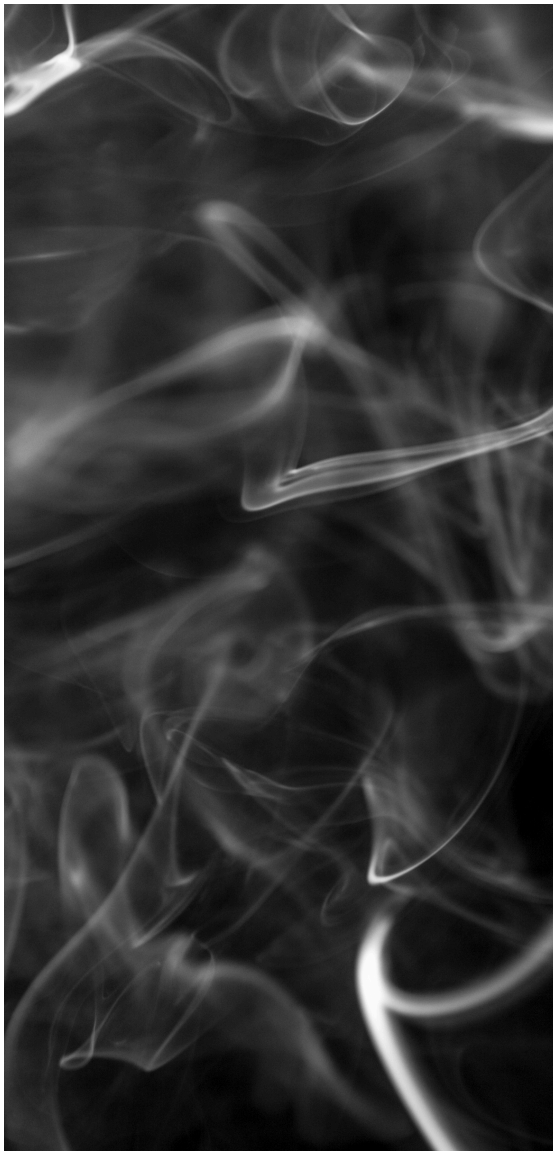
This strategy is effective as it utilizes both dCas9 epigenetic editing to target unmethylated MGMT (7,8), as well as siRNA nanoparticles to target the TERT and EGFR promoters (1,6). This therefore targets the tumor's uncontrolled growth, while hindering the tumor's resistance to regular treatment plans such as chemotherapy due to a methylated MGMT promoter (7). Current strategies of treating glioblastoma include surgical removal, radiation as well as chemotherapy. While these strategies can sometimes be effective, surgical removal can be dangerous within sensitive areas of the brain, while chemotherapy may not always work due to the tumor's unmethylated MGMT promoter. This strategy therefore differs from current treatment strategies as it involves modifying the tumor's genetic makeup, which internally targets the tumor's strength, making treatment strategies such as chemotherapy and radiation much more effective.

1. Alphandéry E. Nano-therapies for glioblastoma treatment [Internet]. U.S. National Library of Medicine; 2020 [cited 2025 Jan 17]. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7017259/#:~:text=Nano%2Ddrugs%20could%20help%20to,GBM%20tumor%20cells%20to%20radiotherapy%2C
2. Author links open overlay panelMartin Bulik a b, a, b, c, d, e, et al. Potential of mr spectroscopy for assessment of glioma grading [Internet]. Elsevier; 2012 [cited 2025 Jan 17]. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0303846712005707
3. Fang Q. The versatile attributes of MGMT: Its repair mechanism, crosstalk with other DNA repair pathways, and its role in cancer [Internet]. U.S. National Library of Medicine; 2024 [cited 2025 Jan 17]. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10814553/
4. Hodges TR, Choi BD, Bigner DD, Yan H, Sampson JH. Isocitrate dehydrogenase 1: What it means to the neurosurgeon: A Review [Internet]. U.S. National Library of Medicine; 2013 [cited 2025 Jan 17]. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3672384/#:~:text=It%20has%20been%20extensively%20shown,overall%20and%20progression%20free%20survival
5. Inda MM;Fan X;Muñoz J;Perot C;Fauvet D;Danglot G;Palacio A;Madero P;Zazpe I;Portillo E;Tunón T;Martinez-Peñuela JM;Alfaro J;Eiras J;Bernheim A;Castresana JS; Chromosomal abnormalities in human glioblastomas: Gain in chromosome 7p correlating with loss in chromosome 10q [Internet]. U.S. National Library of Medicine; [cited 2025 Jan 17]. Available from: https://pubmed.ncbi.nlm.nih.gov/12503074/
6. Lombardo GE;Maggisano V;Celano M;Cosco D;Mignogna C;Baldan F;Lepore SM;Allegri L;Moretti S;Durante C;Damante G;Fresta M;Russo D;Bulotta S;Puxeddu E; Anti- Htert Sirna-loaded nanoparticles block the growth of anaplastic thyroid cancer xenograft [Internet]. U.S. National Library of Medicine; [cited 2025 Jan 17]. Available from: https://pubmed.ncbi.nlm.nih.gov/29563163/
7. Yousefi Y;Nejati R;Eslahi A;Alizadeh F;Farrokhi S;Asoodeh A;Mojarrad M; Enhancing temozolomide (TMZ) chemosensitivity using CRISPR-dCas9-mediated downregulation of O6-methylguanine DNA methyltransferase (MGMT) [Internet]. U.S. National Library of Medicine; [cited 2025 Jan 17]. Available from: https://pubmed.ncbi.nlm.nih.gov/38762829/
8. Zapanta Rinonos S;Li T;Pianka ST;Prins TJ;Eldred BSC;Kevan BM;Liau LM;Nghiemphu PL;Cloughesy TF;Lai A; DCas9/CRISPR-based methylation of O-6-methylguanine-DNA methyltransferase enhances chemosensitivity to temozolomide in malignant glioma [Internet]. U.S. National Library of Medicine; [cited 2025 Jan 17]. Available from: https://pubmed.ncbi.nlm.nih.gov/38224404/

SHAPTHAVI CHRISTY SUTHARSAN |
BACHELOR OF SCIENCE (HONOURS)
CLASS OF 2026

SMOKING/VAPING IN RELATION TO MENTAL HEALTH

EXAMINING THE INTERCONNECTED LINKS BETWEEN SMOKING, VAPING, AND MENTAL HEALTH DISORDERS



The connection between smoking, vaping, and mental health disorders has drawn considerable attention in recent years. This abstract aims to integrate existing research on the relationship among these factors, their reciprocal nature, underlying mechanisms, and the implications for treatment and prevention.

Current research consistently shows that individuals with mental health disorders, including depression, anxiety, and schizophrenia, are more likely to smoke or vape compared to the general population (Asharani, et al., 2020). The prevalence of nicotine use among this group can be linked to various factors, including self-medication. Many individuals turn to nicotine to ease symptoms like anxiety or low mood due to its psychoactive properties. However, while it may initially serve as a means of relief, nicotine use can become overpowering, leading to increased dependence over time. Furthermore, social factors, such as peer influence and exposure to smoking within mental health care settings, can normalize these behaviours among those with psychiatric conditions (Nagawa, et al., 2022).

The link between smoking/vaping and mental illness is not purely coincidental; evidence suggests that nicotine use can worsen existing mental health symptoms (Truong & Cotton, 2023). Studies indicate that smoking is associated with more severe symptoms in individuals with schizophrenia and may complicate the management of anxiety and mood disorders (Quigley & MacCabe, 2019). Additionally, the impact of nicotine on neurotransmitter systems, including dopamine and serotonin, is thought to contribute to both the development and worsening of psychiatric issues.

Vaping, a recent trend, adds complexity to this relationship through biological, psychological, and social factors. Nicotine in e-cigarettes can lead to dependence, while vaping is often seen as a safer alternative but may still reinforce harmful habits. Socially, it can be viewed as more acceptable in certain groups. While some people with mental health conditions see vaping as safer than smoking, emerging evidence suggests it may also contribute to adverse mental health outcomes (Pham et al., 2020). The long-term psychological impacts of vaping are still not well understood, highlighting the need for more research.

Understanding the nuanced relationship between nicotine use and mental health is essential for creating effective and targeted interventions early on. Mental health professionals should prioritize smoking cessation as a key element of treatment for those with psychiatric disorders. Public health initiatives that address the dual issues of nicotine addiction and mental health can improve patient outcomes and promote overall well-being. Moreover, future studies should continue to investigate the causal relationships and long-term effects of smoking and vaping on mental health to develop more adequate prevention and treatment strategies.

Introduction

The use of nicotine products, particularly cigarettes and e-cigarettes, has been a persistent public health concern for decades. However, growing evidence indicates that nicotine use is intricately linked to mental health conditions, particularly among individuals struggling with disorders such as depression, anxiety, and schizophrenia. This relationship is complex and involves both psychological and physiological mechanisms that influence behavior and mental well-being.

Historically, cigarette smoking has been disproportionately high among individuals with psychiatric disorders, and the advent of vaping has further complicated this issue. While some view vaping as a harm-reduction tool, others argue that it may contribute to new and emerging mental health concerns. Understanding the underlying factors driving nicotine use among people with mental illnesses is critical in addressing public health challenges.

This study aims to conduct a systematic review of the current literature to analyze the prevalence, patterns, and impact of nicotine use on mental health, particularly among young individuals. By synthesizing existing research, this paper seeks to contribute to the development of more efficient prevention and intervention strategies tailored to individuals at risk.

Methods

As this is a systematic review, the methodology thoroughly examines existing literature and studies from various institutions. Numerous studies are cross-referenced and analyzed from a cross-sectional perspective to understand the current prevalence, patterns, and correlations between vaping, smoking, and mental health among teenagers, adolescents, and young adults.

The research includes a variety of data collection techniques, with surveys as the primary method. These surveys are carefully designed to ensure the confidentiality of participants, which helps improve the reliability of the data collected. The study aims to identify common themes and trends in nicotine use and mental health outcomes. By analyzing different data sets, it contributes to a comprehensive understanding of the subject.

Results

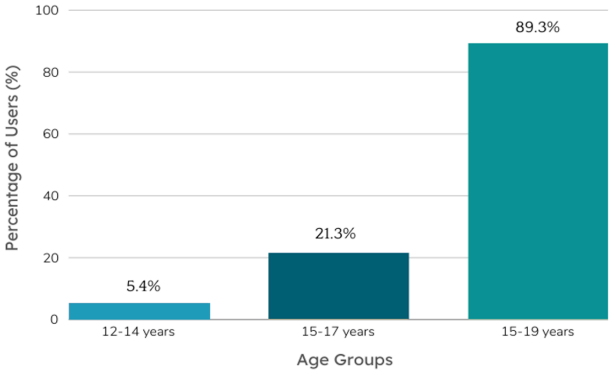


Figure 01. Showcasing the prevalence in Vaping and Nicotine E-liquid usage by Age groups that were recorded and analyzed. These rates were based on survey data that was obtained over a 30-day period.

(Rotermann & Gilmour, 2022)

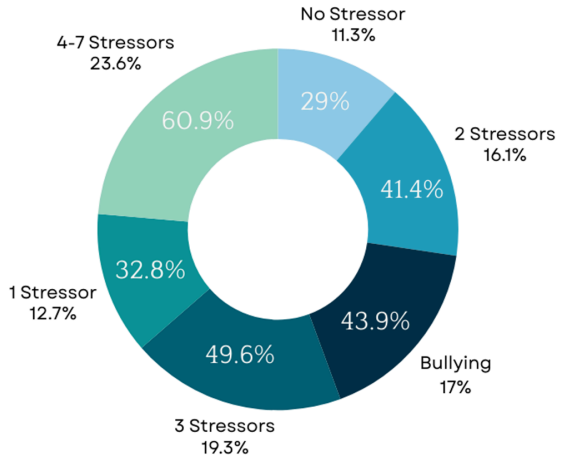
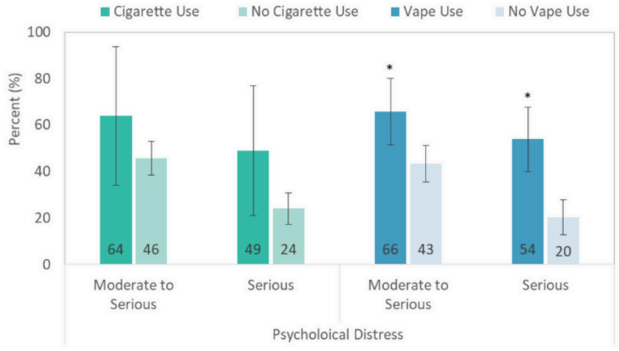


Figure 02. Illustrates the primary reasons why teenagers, adolescents, and young adults are drawn to e-cigarette use. The pie chart displays the total percentage of individuals influenced by each factor, with the labels and values below representing the percentage contribution of each reason within the overall chart.

(Erhabor, et al. 2023)



Source: Ontario Student Drug Use and Health Survey
Note: Error bars represent 95% Confidence Intervals.
* Significant difference determined based on non-overlapping 95% confidence intervals.

Figure 03. This figure is sourced from a Public Health Ontario study examining the impact of COVID-19 on youth mental health, along with cigarette and vape usage. It specifically highlights the psychological distress reported by students in grades 7-12 in Ontario who used cigarettes and vaping devices over the span of a year (2021).

(Public Health Ontario, 2023)

The study results revealed several critical insights into the relationship between nicotine use and mental health. Individuals who smoke or vape were found to have higher incidences of mental health disorders, including depression, anxiety, and stress-related conditions, compared to non-users. The data also showed significant correlations between nicotine use and lower academic performance, as well as challenges in social interactions.

The research highlighted that while e-cigarette use is on the rise among young people, there is still insufficient evidence to establish a direct causal link between vaping and mental health disorders. Instead, the findings pointed to a complex interplay of factors, including psychological stressors, family environments, and peer influence, which could contribute to nicotine use as a coping mechanism for mental distress.

Discussion

The findings from this review emphasize the multifaceted relationship between nicotine use and mental health. The study results revealed several critical insights into this relationship. Individuals who smoke or vape were found to have higher incidences of mental health disorders, including depression, anxiety, and stress-related conditions, compared to non-users. The data also showed significant correlations between nicotine use and lower academic performance, as well as challenges in social interactions. One of the primary takeaways is the increased stressors faced by individuals in modern society, including work pressure, social isolation, and academic stress, driving some to use nicotine products as a form of self-medication. The prevalence of e-cigarette use among youth is particularly concerning, as it reflects a broader trend of seeking quick relief from stress and anxiety without fully understanding the potential long-term consequences.

Psychological factors such as anxiety, depression, and trauma play a significant role in influencing nicotine use. These stressors are often challenging to identify, especially in younger populations, where symptoms may manifest differently. Additionally, family dynamics and social pressures were found to be influential. A supportive family environment can act as a buffer against stress, whereas adverse conditions may increase susceptibility to nicotine use. Peer pressure also remains a critical factor, with many adolescents experimenting with nicotine products to fit in with their social groups.

Academic performance and social variables were also linked to nicotine use, suggesting that mental health support within educational settings could be a valuable intervention. The study calls for more research to explore these relationships further and to develop targeted strategies that address both mental health and nicotine addiction.

Limitations and Next Steps

This study has several limitations. The cross-sectional nature of the data prevents establishing causation between nicotine use and mental health outcomes, and the absence of longitudinal data limits insights into how nicotine's effects may evolve over time. Self-reported surveys, while useful, may introduce bias, such as social desirability influencing responses. To mitigate this bias, future studies could incorporate objective measures, such as biomarkers, physiological data, or behavioral assessments, alongside self-reports to ensure more accurate and reliable results.

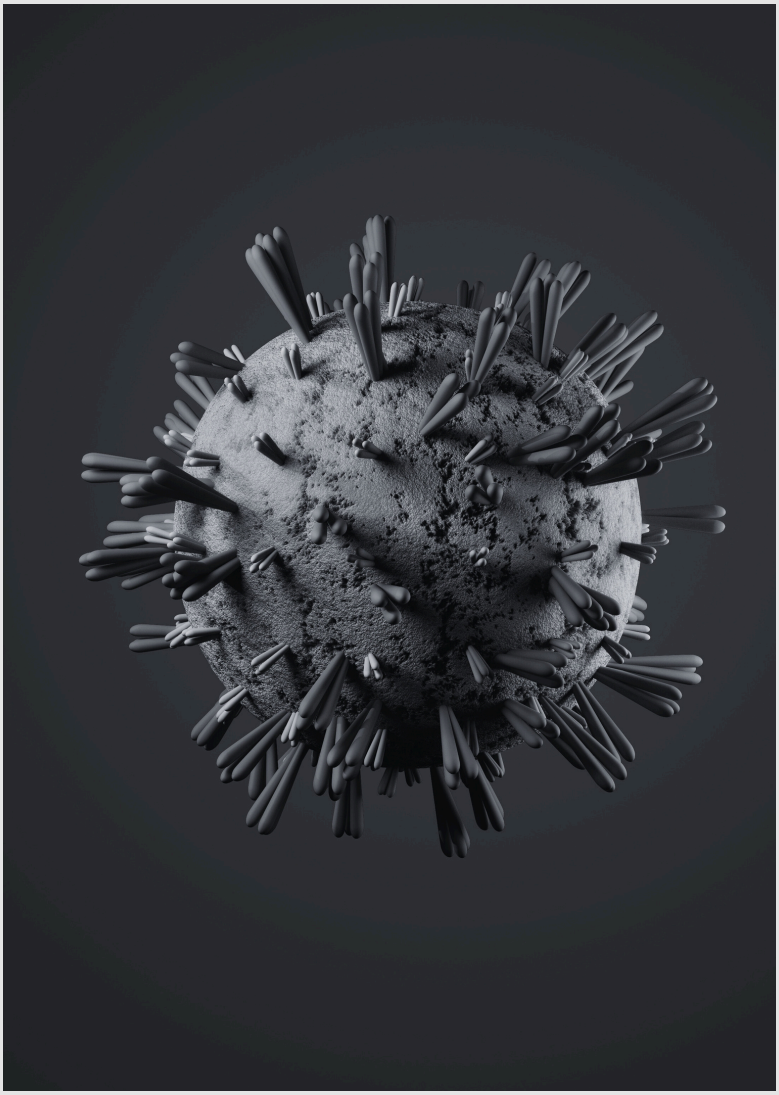
Additionally, the study samples lacked full representation of diverse socioeconomic statuses, cultural backgrounds, and family histories, potentially leading to overgeneralized conclusions and unaddressed confounding variables. These constraints highlight the need for more comprehensive studies with broader sample populations and improved methodologies. Future research should focus on ensuring greater diversity in sample populations by considering factors such as age, geographic location, and varied socioeconomic conditions. This would help in capturing a more accurate picture of the relationship between nicotine use and mental health outcomes across different groups.

To address these gaps, future research should incorporate both cross-sectional and longitudinal studies to better understand the causal relationships between nicotine use and mental health. Longitudinal studies would be particularly useful in tracking changes in mental health over time and in observing how nicotine use may either contribute to or worsen mental health conditions. Expanding sample diversity and controlling for confounding variables will enhance result accuracy. Additionally, exploring biological and neurological perspectives on nicotine's impact on mental health, including its effects on neurotransmitters, addiction potential, and brain development, is essential. This includes comparing the chemical impacts of vaping versus smoking, particularly in terms of their neurological effects, such as dopamine regulation, their potential for addiction, and their long-term effects on cognitive and emotional functioning. These approaches will contribute to more practical prevention and treatment strategies, ultimately improving outcomes for those facing nicotine addiction and mental health challenges.

1. Asharani, P. V., Ling Seet, V. A., Abdin, E., Siva Kumar, F. D., Wang, P., Roystonn, K., Lee, Y. Y., Cetty, L., Teh, W. L., Verma, S., Mok, Y. M., Fung, D. S. S., Chong, S. A., & Subramaniam, M. (2020). Smoking and Mental Illness: Prevalence, Patterns and Correlates of Smoking and Smoking Cessation among Psychiatric Patients. International journal of environmental research and public health, 17(15), 5571. https://doi.org/10.3390/ijerph17155571
2. Nagawa, C. S., Pbert, L., Wang, B., Cutrona, S. L., Davis, M., Lemon, S. C., & Sadasivam, R. S. (2022). Association between family or peer views towards tobacco use and past 30-day smoking cessation among adults with mental health problems. Preventive medicine reports, 28, 101886. https://doi.org/10.1016/j.pmedr.2022.101886
3. Pham, T., Williams, J. V. A., Bhattarai, A., Dores, A. K., Isherwood, L. J., & Patten, S. B. (2020). Electronic cigarette use and mental health: A Canadian population-based study. Journal of affective disorders, 260, 646–652. https://doi.org/10.1016/j.jad.2019.09.026
4. Quigley, H., & MacCabe, J. H. (2019). The relationship between nicotine and psychosis. Therapeutic advances in psychopharmacology, 9, 2045125319859969. https://doi.org/10.1177/2045125319859969
5. Truong , M., & Cotton, E. (2023, October). The impact of vaping on Adolescent Mental Health. Australian Institute of Family Studies. https://aifs.gov.au/resources/policy-and-practice-papers/impact-vaping-adolescent-mental-health
6. Rotermann, M., & Gilmour, H. (2022, July 20). Correlates of vaping among adolescents in Canada. Statistics
7. Canada. https://www150.statcan.gc.ca/n1/pub/82-003-x/2022007/article/00003-eng.htm
8. Erhabor, J., Boakye, E., Osuji, N., Obisesan, O., Osei, A. D., Mirbolouk, H., Stokes, A. C., Dzaye, O., El-Shahawy, O., Rodriguez, C. J., Hirsch, G. A., Benjamin, E. J., DeFilippis, A. P., Robertson, R. M., Bhatnagar, A., & Blaha, M. J. (2023). Psychosocial stressors and current e-cigarette use in the youth risk behavior survey. BMC public health, 23(1), 1080. https://doi.org/10.1186/s12889-023-16031-w
9. Ontario Agency for Health Protection and Promotion (Public Health Ontario). (2023, December). Impact of the COVID-19 Pandemic on Youth Smoking, Vaping, and Mental Health . Public Health Ontario. https://www.publichealthontario.ca/-/media/Documents/nCoV/main/2023/covid-19-impact-pandemicyouth-tobacco-smoking-vaping.pdf?rev=99274434e74342a996d6fcdf753099ca&sc_lang=en

UTILIZING IMMUNOTHERAPEUTIC MRNA VACCINES AGAINST GLIOBLASTOMA

JOANNA ZHAO[1]
ANITA ALIZADEH[2]
MONIS SAYYID[3]
GRAYSON CESSNA[4]
ANDY LU[5]



1. DOGWOOD DIPLOMA, YEAR 3, MARIA MONTESSORI ACADEMY
2. HONOURS PSYCHOLOGY, NEUROSCIENCE, AND BEHAVIOUR, YEAR 2, MCMASTER UNIVERSITY
3. HONOURS SPECIALIZATION BIOCHEMISTRY AND PATHOLOGY OF HUMAN DISEASE, YEAR 3,
4. UNIVERSITY OF WESTERN ONTARIO
5. PSYCHOLOGY, YEAR 3, UNIVERSITY OF NORTH CAROLINA CHARLOTTE
6. HONOURS SPECIALIZATION DEVELOPMENTAL COGNITIVE NEUROSCIENCE, YEAR 2, UNIVERSITY OF WESTERN ONTARIO

Glioblastoma (GBM) is characterized as a highly aggressive central nervous system (CNS) malignancy with a poor prognosis, driven by its heterogeneity. The abnormal astrocytic cells and blood vessels, areas of heavy necrosis, and rapid cell division contribute to GBM resistance against conventional therapies. FDA-approved treatments—surgical resection, radiation therapy, and temozolomide—show effectiveness, yet are aggressive and result in irreversible damage to surrounding brain tissue. In contrast, mRNA-based immunotherapy aims to target glioblastoma cells precisely, potentially reducing tissue damage. However, further studies are needed to assess its long-term safety and efficacy. Research led by Dr. Elias Sayour at the University of Florida (UF) has made substantial progress towards the development of mRNA-based vaccines for GBM treatment, developing a novel lipid nanoparticle structure to further support mRNA delivery, improving the vaccine's efficacy. These mRNA vaccines function by encoding individualized, tumour-specific antigens that stimulate the patient's immune system to attack active GBM cells. Contrastingly, conventional treatment emits high doses of radiation that damage the DNA within the tumour cells, preventing cell growth, but damaging surrounding cognitive tissue. Ongoing studies at UF include preclinical trials utilizing brain tumours in animal models that share characteristics resembling those of human GBM. The mRNA vaccine elicited a robust immune response with significant tumour regression and extended survival in animal models—suggesting that this approach holds the potential to offer a safer, personalized, and effective alternative to conventional treatment. Limitations within the mRNA vaccine can include vulnerability to degradation, a poor delivery system, and heavy reliance on variable factors; like the patient's immune system and immunosuppressive cells. Researchers at UF are currently undergoing trials, creating a smoother delivery system with layered lipid nanoparticles, improving efficacy and mRNA storage. Current studies, including pediatric clinical trials, hold promise for revolutionizing GBM therapy and substantially improving prognosis.

Glioblastoma (GBM), one of the most commonly diagnosed central nervous system (CNS) oncological conditions, constitutes 14.5% of all CNS tumors and 48.6% of malignant CNS neoplasms (1). GBM has a poor prognosis, with a median survival rate of 14 months (2). It is typically distinguished by rapid-growth, expansion and infiltration into surrounding brain tissue (3).

Although GBM was first discovered in the 1800s (4), the FDA has only recognized a few treatments—the most common being surgical resection, followed by radiation therapy (RT) and temozolomide (TMZ). TMZ is medication used to treat GBM multiforme in patients with newly diagnosed or returning tumours. Outside of temozolomide (TMZ), the FDA has approved four drugs and one medical device for treating high-grade gliomas: carmustine wafer implants, lomustine, intravenous carmustine, bevacizumab, and tumor treatment fields (TTFields) (5, 6). While these conventional therapies can be effective, they are highly aggressive and often cause permanent damage to surrounding cognitive tissue. In contrast, GBM remains resilient against treatment due to the unique biology of its cells—which have the capabilities to evade conventional treatment effects through increased resistance to cell death and rapid regeneration of cancerous cells (7), highlighting the need for novel therapeutic strategies (3). Immunotherapy, particularly mRNA-based cancer vaccines, has shown promise towards presenting a groundbreaking, effective solution.

Led by Dr. Elias Sayour, a team of researchers at the University of Florida (UF) has made significant progress toward mRNA cancer vaccines for GBM (8). Preclinical studies utilized mouse models to evaluate the vaccine's efficacy by measuring survival rate extension, tumour shrinkage, and immune system activity. Researchers created synthetic brain tumours within mice, analogous to human glioblastomas. Following the administration of the mRNA vaccine, the model mice showcased strong immune responses, with recorded increases in immune system activity within the tumour—leading towards significant GBM shrinkage and extended survival rates (8). These promising results laid the foundation for the following stage of clinical studies, where UF researchers conducted clinical trials involving dogs diagnosed with naturally-occurring brain tumours that closely mirrored those of human GBM in terms of tumour behaviour and immune response (8, 9). The study was conducted with ten dogs who received the mRNA vaccine.

Post-vaccination, the dogs demonstrated rapid immunological changes within their tumours, indicating the host immune system reacted with a robust response. Most significantly, these dogs experienced a substantial extension in survival time—nearly fourfold the previous prognosis for canine brain cancer patients, with pre-injection median survival being 30-60 days, and post-injection survival length being extended to a median of 139 days. (8, 9). However, it is essential to note that UF has released limited data or statistical analyses on these findings, making further validation necessary.

The consistent results from mouse models and canine participants provided strong evidence of the vaccine's potential efficacy in humans. Building on the promising results from animal trials, the UF team aims to test the vaccine's effectiveness in pediatric patients, leveraging the same mRNA technology that encodes individualized antigens to stimulate the immune system's response against glioblastoma (8).

These mRNA vaccines encode tumour-specific antigens, which prompt the host's immune system to attack the specified GBM. This is achieved by delivering synthetic messenger RNA (mRNA) into the immune system. Once administered, the mRNA is taken by antigen-presenting cells via endocytosis; upon entering the specified cells, it is further translated into encoded protein antigen (10). The cell's ribosomes process the mRNA, producing specific proteins that are presented on the plasma membrane, binding to the Major Histocompatibility Complex (MHC) molecules and directing the immune system's attention to the tumor. Preclinical studies and early-phase trials involved researchers at the UF who administered a personalized mRNA vaccine to four adult patients with GBM (8). The vaccine rapidly reprogrammed the patients' immune systems to target their tumors, transforming the TME to immunologically active within 48 hours. These studies have shown that mRNA vaccines can elicit a strong immune response from the patient's body, leading to GBM regression and prolonged survival.

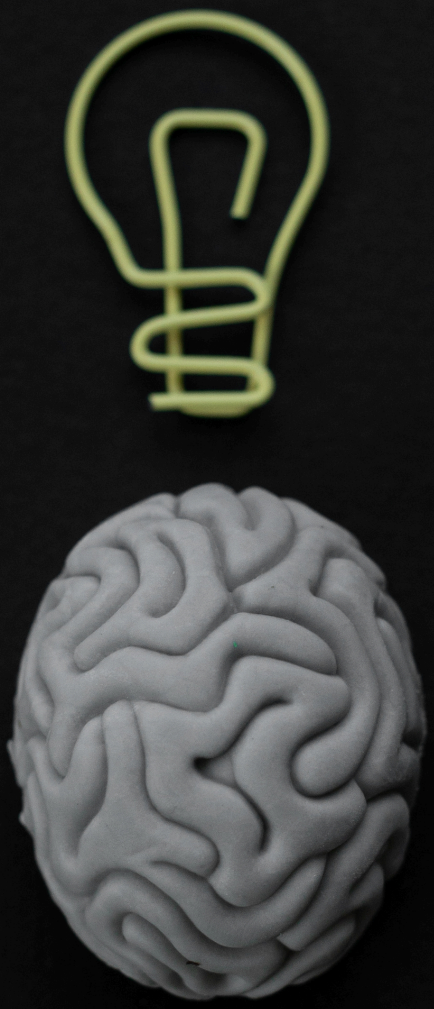
The procedure for mRNA vaccine administration is typically instigated by the surgical removal of GBM tissue from the patient. With this excised tumour, researchers can extract total RNA, which includes mRNA, tRNA, rRNA, as well as snRNA, miRNA, and lncRNA, providing a complete genetic blueprint of the tumor's unique antigens.

This RNA serves as the foundation for the creation of an mRNA vaccine individualized to a specific cancer profile (11). The extracted RNA is then expanded to manufacture the unique mRNA and carry specific instructions regarding protein synthesis (8, 9). This mRNA is then encapsulated with lipid nanoparticles, protecting and facilitating its transition into the specified cells. The UF researchers have compiled a unique nanoparticle design capable of carrying mRNA strands within its internal lipid layers. In contrast, typical mRNA vaccines have a spherical core, allowing for the lipid nanoparticles to hold roughly 2.8 mRNA molecules per nanoparticle, thereby restricting the vaccines efficacy (9, 12). Dr. Sayour and his team have developed a nanoparticle with layered lipids, a unique structure that can hold more mRNA molecules per nanoparticle, streamlining transportation and increasing effectiveness (8).

This innovative nanoparticle design not only enhances mRNA delivery but also ensures a more efficient immune response. Once administered, the mRNA-lipid nanoparticles are taken by the host immune system's antigen-presenting cells (APCs) via endocytosis. Inside these cells, the mRNA is released into the cytoplasm, translated by ribosomes, and manufactured into tumour-specific antigens—proteins that can mirror those found on the patients glioblastoma cells (10, 13). Subsequently, the proteasome processes this synthesized antigen, which further degrades the protein into smaller forms of antigenic peptide fragments, typically referred to as epitopes (10, 15). A portion of these epitopes are transported through the endoplasmic reticulum, loaded on MHC class I molecules, and are transported to the APC surface to be displayed. They are promptly recognized by CD8+ cytotoxic T cells. CD8+ T cells require co-stimulatory signals from APCs for full activation; a primary co-stimulatory route involves CD28 receptors on T cells binding to CD80 (B7-1) or CD86 (B7-2) ligands on APCs (16). This pathway is vital towards the activation of cytotoxic T lymphocytes (CTLs), which damage and kill GBM cells. Additional epitopes are placed onto MHC class II molecules for transportation to be presented on the surface of the cell as well, acting as signals to be recognized by CD4+ T helper cells—which will further activate the patient's immune system to emit more B cells and CTLs through a regulated process, guided by cytokines like interleukin-2 (IL-2) and interferon-gamma (IFN-γ). IL-2 is a growth factor that promotes the differentiation of T cells, including CTLs, indirectly supporting B cell activation and antibody production. IFN-γ is a cytokine produced by Th1 cells that activate macrophages and enhance antigen presentation. (10, 17).

The rapid development of the mRNA vaccine by UF showcases a promising advancement in glioblastoma treatment, introducing a novel lipid nanoparticle structure designed to enhance mRNA delivery. Utilizing this design, the UFO researchers conducted preclinical trials in mice and dogs, demonstrating promising results, showing tumor shrinkage and extended survival, transforming the tumor microenvironment into an immunologically active state. These mRNA vaccines reprogram the immune system to recognize and attack glioblastoma cells, synthesizing within the APC's of the patient. While further validation is necessary, these findings highlight the potential of mRNA vaccines as a groundbreaking therapeutic strategy for glioblastoma.

1. Grochans S, Cybulska AM, Simińska D, Korbecki J, Kojder K, Chlubek D, et al. Epidemiology of Glioblastoma Multiforme–Literature Review. Cancers. 2022 May 13;14(10):1–32.
2. Mohammed S, M D, T A. Survival and quality of life analysis in glioblastoma multiforme with adjuvant chemoradiotherapy: a retrospective study. Reports of Practical Oncology and Radiotherapy [Internet]. 2022 Dec 29;27(6):1026–36. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9826661/
3. Davis M. Glioblastoma: Overview of Disease and Treatment. Clinical Journal of Oncology Nursing. 2016 Oct 1;20(5):S2–8
4. Sharma HS, Muresanu DF, Castellani RJ, Nozari A, Lafuente JV, Tian ZR, et al. Pathophysiology of blood-brain barrier in brain tumor. Novel therapeutic advances using nanomedicine. International Review of Neurobiology. 2020;1–66,
5. Fisher JP, Adamson DC. Current FDA-Approved Therapies for High-Grade Malignant Gliomas. Biomedicines [Internet]. 2021 Mar 1;9(3):324. Available from: https://www.mdpi.com/2227-9059/9/3/324/htm
6. Temozolomide (Oral Route) Description and Brand Names - Mayo Clinic [Internet]. www.mayoclinic.org. Available from: https://www.mayoclinic.org/drugs-supplements/temozolomide-oral-route/description/drg-20066228
7. Siva S, Filipczak N, Li X, Md. Abdus Subhan, Parveen F, Janaina Artem Ataide, et al. Mechanisms of Resistance and Current Treatment Options for Glioblastoma Multiforme (GBM). Cancers [Internet]. 2023 Apr 1;15(7):2116–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10093719/
8. UF-developed mRNA vaccine triggers fierce immune response to fight malignant brain tumor» Cancer Center» UF Health Cancer Center» University of Florida [Internet]. Ufl.edu. 2024 [cited 2025 Feb 28]. Available from: https://cancer.ufl.edu/2024/05/01/uf-developed-mrna-vaccine-triggers-fierce-immune-res ponse-to-fight-malignant-brain-tumor/
9. mRNA Vaccine Boosts Immune Response Against Glioblastoma [Internet]. Cancer.gov. 2024 [cited 2025 Feb 28]. Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2024/glioblastoma-mrna-vacci ne-layered-nanoparticle
10. Zdeslav Strika, Karlo Petković, Likić R. Effectiveness and Safety of mRNA Vaccines in the Therapy of Glioblastoma. Journal of Personalized Medicine [Internet]. 2024 Sep 19;14(9):993. Available from: https://www.researchgate.net/publication/384149464_Effectiveness_and_Safety_of_mRNA_Vaccines_in_the_Therapy_of_Glioblastoma,
11. Iulia Tapescu, Madsen PJ, Lowenstein PR, Castro MG, Bagley SJ, Fan Y, et al. The transformative potential of mRNA vaccines for glioblastoma and human cancer: technological advances and translation to clinical trials. Frontiers in Oncology. 2024 Sep 27;14.
12. GenScript Expert. Uncovering Nucleic Acid Payload and Size of Lipid Nanoparticles via a Single Nanoparticle Analyzer [Internet]. Genscript.com. 2023 [cited 2025 Mar 3]. Available from: https://www.genscript.com/invited-articles-news/uncovering-nucleic-acid-payload-and-si ze-of-lipid-nanoparticles-via-a-single-nanoparticle-analyzer.html
13. Gote V, Bolla PK, Kommineni N, Butreddy A, Nukala PK, Palakurthi SS, et al. A Comprehensive Review of mRNA Vaccines. International Journal of Molecular Sciences. 2023 Jan 31;24(3):2700.
14. Kaczmarek M, Poznańska J, Fechner F, Michalska N, Paszkowska S, Napierala A, et al. Cancer Vaccine Therapeutics: Limitations and Effectiveness—A Literature Review. Cells [Internet]. 2023 Aug 28;12(17):2159. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10486481/
15. Chaudhary N, Weissman D, Whitehead KA. mRNA vaccines for infectious diseases: principles, delivery and clinical translation. Nature Reviews Drug Discovery [Internet]. 2021 Aug 25;20(11). Available from: https://www.nature.com/articles/s41573-021-00283-5
16. Aai.org. [cited 2025 Mar 3]. Available from: https://journals.aai.org/jimmunol/article/179/10/6494/75644/Memory-CD8-T-Cells-Requi re-CD28-Costimulation1?
17. Jorgovanovic D, Song M, Wang L, Zhang Y. Roles of IFN-γ in tumor progression and regression: a review. Biomarker Research. 2020 Sep 29;8(1).



MCMASTER BRAIN
RESEARCH SOCIETY