
The Journal of the IYNA

July 2025
VOL. 9 ISSUE 4

FEATURED ARTICLES

'Nitrous Oxide, Not Ketamine: An Alternative to Psychedelic Therapy'
- Ashley Keith

'The Effects of Space Exploration On The Brain'
- Evelyn Gaspich

'Media-Driven Beauty Standards: The Impact on Consumer Behavior, Body Image, and Mental Health'
- Mariangel Cisneros

Contents

INTRODUCTION

Letter from the Editors IYNA Editorial Team Page 4

GENERAL NEUROSCIENCE

The Neurological Effects of Bullying Joy Kennemer Pages 5-II

This article explores how adolescence, a critical period of self-discovery, is especially vulnerable to the harmful effects of bullying. Influenced by social media, peer pressure, and societal expectations, bullying is common among teens and can have serious, lasting consequences. It can lead to long-term neurological changes, mental health disorders, and even physical illness, highlighting the need for greater awareness and prevention during this formative stage of life.

The impact of parenting styles on structuring Beverly Tadeo
neuroplasticity in childhood and adolescence Pages 12-17

This article examines how parenting styles and early environments significantly influence a child's brain development through neuroplasticity. Since children begin learning at a very young age, the way they are raised can have lasting effects. Supportive parenting promotes healthy cognitive and emotional growth, while toxic or neglectful environments may lead to long-term changes in brain structure and function, resulting in behavioral and cognitive issues later in life. The article emphasizes the importance of a positive, stable environment for optimal brain development.

The effects of space exploration on the brain Evelyn Gaspich Pages 18-25

This article explores the various effects of space exploration on the brain, highlighting both its promise and its risks. While space offers opportunities to explore life beyond Earth and understand the universe's origins, it also poses serious challenges. The most significant dangers include space radiation, isolation and confinement, and microgravity.

Media-Driven Beauty Standards: The Impact on Mariangel Cisneros
Consumer Behavior, Body Image, and Mental Health Pages 26-33

This paper examines how mass media promotes unrealistic beauty ideals that significantly impact consumer behavior, body image, and self-esteem. These flawless and often unattainable standards pressure individuals, especially women, to purchase beauty products or undergo cosmetic procedures. Constant exposure to these

ideals can create a harmful cycle where self-worth becomes tied to appearance and social acceptance. The paper emphasizes the need to understand how media-driven beauty standards influence individual and cultural perceptions to address their negative effects.

Is there increased hippocampal function in individuals who practice Abrahamic religions?	Joy Chastity Spencer-Thomas	Pages 34-40
--	-----------------------------	----------------

This paper explores the connection between the hippocampus and spirituality through the lens of neurotheology, which studies religious experiences from a neurological perspective. The hippocampus is shown to play a role in spiritual and moral reasoning. Research suggests that practices like meditation, prayer, and communal religious activities can enhance hippocampal function, promote emotional stability, and strengthen social bonds. Examples include altered brain activity during Christian glossolalia and Muslim prayer. While findings highlight potential benefits, current research faces challenges such as cultural bias and limited methodology, underscoring the need for broader studies, including in non-religious contexts.

Nitrous oxide, Not Ketamine: An Alternative to Psychedelic Therapy	Ashley Keith	Pages 41-50
--	--------------	----------------

This paper sheds light on the potential of nitrous oxide (“laughing gas”) as a treatment for mental illness, particularly depression. While commonly used in surgery, dentistry, and even whipped cream canisters, nitrous oxide is also used recreationally for its dissociative effects. Due to its lower potency and favorable safety profile, nitrous oxide may offer a safer, more accessible alternative for rapid-acting antidepressant treatment.

DISEASES AND DISORDERS

Virtual Reality and Its Impact on Alzheimer’s Disease	Samuel Mayers	Pages 51-60
---	---------------	----------------

This article examines the roles of mitochondrial dysfunction and astrocyte deficiencies in the development of schizophrenia, a neurodevelopmental disorder characterized by cognitive, emotional, and behavioral impairments. Since astrocytes are crucial for synapse regulation, brain homeostasis, and prefrontal cortex development, their impairment contributes to cognitive deficits. The interconnected dysfunction of mitochondria and astrocytes may underlie key schizophrenia symptoms, offering potential pathways for new therapeutic strategies.

The Role of Astrocytes in Schizophrenia	Jesus Juan	Pages 61-66
---	------------	----------------

Direct Correlation Between Sleep Deprivation and Parkinson's Disease Onset Through Glymphatic System Dysfunction	Arian Phillips	Pages 67-74
--	----------------	----------------

This paper explores Parkinson's disease, the second most common neurodegenerative disorder, which is driven by alpha-synuclein plaque buildup and dopamine neuron loss. A key but often overlooked risk factor is sleep disturbance. Sleep deprivation contributes directly to neurodegeneration by impairing the brain's waste clearance system, causing mitochondrial dysfunction, oxidative stress, and genetic changes that accelerate PD onset and progression. Beyond being a risk factor, inadequate sleep also leads to cognitive decline and shortened telomeres, further linking sleep to PD development and severity.

Unraveling the Link: Smoking as a Modifiable Risk Factor for Dementia	Prakhar Singhania	Pages 75-81
---	-------------------	----------------

This article reviews the strong link between smoking and increased dementia risk, highlighting smoking as a major preventable contributor to neurodegeneration. Smoking raises dementia risk by 30-40%, contributing to about 14% of global cases, through mechanisms like oxidative stress, inflammation, and brain vascular damage. The review emphasizes the need for public health strategies, such as education, screening, and access to cessation programs, to reduce dementia prevalence and improve long-term brain health.

CONTRIBUTORS PAGES *pages 82-83*

· INTRODUCTION ·

Letter From the Editors

Journal Leadership

Dear Readers,

Welcome to the fourth issue of the 9th volume of the IYNA Journal! We greatly appreciate your readership, continued or new. We have worked hard at producing more high-quality articles for everyone to read and encouraging a growing number of high school students from around the world to submit their neuroscience findings, research, and/or interviews to the journal. We've hand-picked a special few to showcase in this month's journal.

We have been receiving many wonderful articles from you guys. It is clear how much the journal is improving as we review each article submission. We would just like to thank everyone who has submitted articles to this issue and prior issues alike. Without your dedication and hardwork, we would not be able to spread the word about the amazing diversity in subject matter that neuroscience, and neuroethics specifically, has to offer. With that being said, here are some previews of the essays published this month:

Ashley Keith explores the Nitrous Oxide as an alternative to Psychedelic Therapy, Evelyn Gaspich examines the effects of space exploration on the brain, and Mariangel Cisneros sheds light on media-driven beauty standards.

We would like to recognize all of our dedicated editors for helping us make this issue the success that it is. You can see all of their names and positions on our Contributors page. If you have any questions, comments, or suggestions for us, please email apan@youthneuro.org. We hope you enjoy reading this issue as much as we enjoyed editing it!

Best Regards,

Annie Pan - IYNA Journal Editor-In-Chief

Ashvin Kumar - Managing Editor

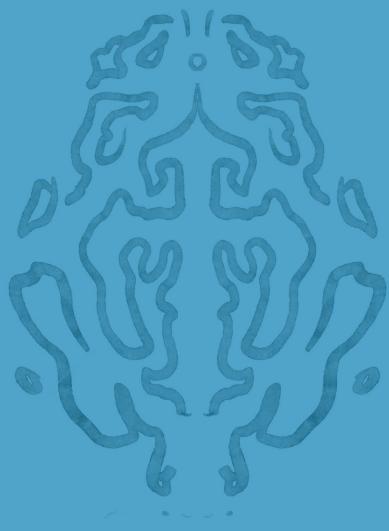
Riyaa Sri Ramanathan - Head of Assembly

Aleksandra Dubno - Head of Outreach

Ananyaa Karthikeyan - Head of Events

Ana Beatriz Araujo - Head of Translation

Shrika Vejandla - Head of Journalists



GENERAL NEUROSCIENCE

The Neurological Effects of Bullying

Joy Kennemer

Abstract

Adolescence is a vulnerable time for young people because they go through many life-changing phases. During this period, they search to find themselves in this ever-changing world. However, finding one's self can have a negative impact because of many things and bullying is one of them. Bullying is common among adolescents because of social media influence, peer pressure, and social standards. Regardless of the reason, this can heavily impact individuals and can result in long-term neurological effects. The effects of bullying can cause brain morphology, mental health disorders, and physical illness.

Introduction

Approximately 19.2 % of students in America get bullied once they enter middle school to high school (6th - 12th grade) [1]. Bullying creates a hostile environment that disrupts order. Bullying is when someone receives unwanted behavior from someone else. People tend to bully others when they possess something the others don't have. The power imbalance between those dynamics could be physical strength, popularity, or access to embarrassing information. It can be categorized into four types: social, cyber, physical, or verbal. Verbal bullying is sharing or writing foul things. This includes teasing, taunting, inappropriate sexual comments, name-calling, and threatening to cause harm. Social bullying is doing something to hurt the relationship someone has with others or their reputation. This bullying includes not including someone on purpose, public humiliation, and spreading rumors. Physical bullying is physically hurting someone or their possession. This type of bullying includes hitting/kicking/punching, spitting, tripping/pushing, taking or breaking someone's things, and making obscene gestures. Cyberbullying is a type of bullying that is done online. This includes slander through the media.

Furthermore, it is important to know the lingering effects of these numerous types of bullying because it is so common throughout adolescence [2]. Bullying during the adolescent stage can present deteriorating effects on the person's mental and physical health as they continue to progress into adulthood. These effects are known as chronic peer victimization.

Adolescent

Adolescence is considered late childhood and early adulthood, reflecting the ages between 10 and 19. During adolescence, many things happen throughout the brain: synapses (where neurons communicate with each other) are eliminated, white matter volume increases, and neurotransmitters

change. White matter helps us process information and neurotransmitters send the neuron's message to the muscles to act. Blakemore's social brain and development study states a developmental change in the cortical circuits occurring throughout this transitional stage. The cortical circuit is crucial for survival since it enables us to assess and evaluate our environment, plan actions, learn from experiences, regulate emotions, and think critically [3]. When development arises in the brain during the pubescent stage, gray matter matures back to the front of the brain. It reaches full capacity in the primary sensorimotor cortex which perceives sensory details from the body regarding temperature, proprioception (self-movement, force, and body position), touch, texture, and pain [4]. The gray matter finally covers higher areas such as the dorsolateral prefrontal cortex, the inferior parietal gyrus, and the superior temporal gyrus. These areas control cognitive function and develop later in life. The brain goes through a lot of change making it more vulnerable during this critical time. Bullying during this susceptible period can present effects on mental and physical health in the long term[5].

Mental and Physical Health

A study conducted by Wolke, D., Woods, S., Bloomfield, L., & Karstadt, L. [6] demonstrated that people who were bullied whether it was a short amount of time or a long time throughout childhood now report having mental health disorders including depression, anxiety, and problems with their sleep. When someone is bullied throughout their childhood, it can present anatomical and physiological alterations in the brain either by enlarging areas or reducing them. The most common mental disorder for peer victimization is social phobia, when social interactions cause significant anxiety, self-consciousness, or embarrassment. [7] This can also lead to depression, general anxiety, and internalizing and externalizing symptoms[8]. Symptoms of internalizing behaviors of adolescence include sadness, anxiety, and loneliness. In contrast, externalizing behaviors showcase symptoms of aggression and hyperactivity[9]. Mental distress is linked to physical malaise or harmful behaviors. Depression is cognate with many chronic illnesses such as diabetes, asthma, cancer, cardiovascular disease, and arthritis. Anxiety can cause someone to hyperventilate, which can lead to feeling lightheaded and nauseous.

Additionally, it is arduous to treat chronic illness in individuals who have mental health illnesses leading to worsening of their conditions. Studies suggest that 50% to 80% with mental conditions have problems with their sleeping habits, including either insomnia or sleep apnea. Smoking and drinking are more common in people who have neurotic disorders than those who are mentally stable [10]. It is essential to know how bullying plays a part in the brain structure, especially in the development of cognitive and emotional functions.

Studies & Data

Relating to the link between bullying and cognitive complications, a recent study [11] provides evidence of how constant bullying can impair brain function and structure over the years. Bullying is linked to many mental health issues. Constant bullying throughout childhood can

persist in chronic effects on the brain as the individual advances into adulthood. It has been reported there are signs of cognitive impairments concerning children who were targeted for bullying. Cognitive impairment delays a person's thinking, action, and adaptation to their environment. An experiment was conducted longitudinally through the Adolescent Brain Cognitive Development (ABCD) dataset to evaluate children exposed to bullying. This study determined the children who were bullied have poor cognitive execution and display low subcortical volume, cortical surface area, and cortical thickness zone comprised in cognition areas, the prefrontal cortex and hippocampus, and emotion processing areas, the putamen and amygdala. These alterations to the brain show the effect of bullying on cognitive results. The experiment participants are between 9 and 10 years old and were assembled from 21 sites throughout the United States. The ABCD study first created a baseline, classifying it as year 1, and another annual review assessment was conducted, classifying it as year 3. The test measures participants' age, height, weight, sex, race/ethnicity, guardian's education level, and guardian's salary. The conductors questioned the caregiver if their child experienced bullying at school or in their neighborhood. If they responded yes on both assessments, they met the criteria for being bullied.

In addition, if they respond with a no to the question for both assessments, they are perceived as not being bullied. The participants' guardians answered questions with a yes for the first assessment but no to the following evaluation, they were sanctioned from the experiment. The proctor viewed the child's reading, memory, processing speed, inhibitory control and attention, and vocabulary. The caregiver also answered questions based on the baseline child's behavior regarding the child's mental health status. They used T1-weighted MP-RAG to take images of the brain at different points. T1-weighted MP-RAG is used for MRI images of the brain in high contrast to make it easier to spot problems [12]. When analyzing the brain, they used Free Software, which depicts the brain's surface area, the cortex's thickness, and the subcortical regions' volume. Different parts of the brain were examined using this software. There were 645 participants in the experiment, 323 of the children were classified as being bullied and 322 of the children were classified as not being bullied. Both of these groups had background similarities. The outcome of the study is that bullied adolescents present larger hippocampal volumes than non-bullied victims. The right hippocampal is in control of the visual, and spatial learning and memory. Over time, the left cerebral white matter volume only increased in non-bullied children. Bullying hinders the growth of white matter usage in the left cerebral affecting cognitive functions. Bullied children present larger cortical volumes in the left entorhinal, left superior parietal, and right fusiform than non-bullied children. The left entorhinal is a gateway for information going in and out of the hippocampal formation. The left superior parietal lobe assists with spatial awareness, movement coordination, and sensory processing. The right fusiform helps with facial recognition. The children's brains affected by the bullying present growth in surface area between visits in regions such as the right temporal pole and left rostral anterior cingulate. The right temporal pole helps with remembering and learning nonverbal information [13]. The left rostral anterior cingulate processes normal and abnormal fear [14]. The expansion of the right fusiform is linked to lower cognitive scores. Bullied victims exhibited thinner cortices in the left hemisphere, including the left middle temporal gyrus and precentral gyrus. The left hemisphere is mainly responsible for speech and processing language. The left middle temporal gyrus displayed a higher thinning of the bullied cohort by year 3.

The consequences of thinner cortices are bad inhibitory control and low attention scores. This can cause bullied victims to have difficulty controlling their urges which can lead them to do unintentional harm as they continue to grow if not treated. The change in the physical properties of the brain, such as thinning cortices and conversion in subcortical regions, emphasize the weight of emotional and psychological bullying victims encounter, as statistics prove the higher rate of depression and anxiety among this group.

One study focused on the differences and similarities between adolescents and young adults with depression compared to those without mental health disorders through the grey matter volumes. Those with depression present larger grey matter volume in the dorsolateral prefrontal cortex. Those with depression have smaller grey matter in the hippocampus. In adolescents with depression who have more expanded volumes in the prefrontal complex, this can create a setback with brain maturation or have greater neuroplasticity. Neuroplasticity is when the brain adjusts to the stimulation of learning and experience. Mental health problems are due to the difficulty in the communication of the neurons. [15].

According to Gonalzez, the Principal Investigator of a rising research group on "Cyberbullying and emotional intelligence", cyber victims have a higher release of cortisol and greater perceived stress compared to cyber bullies and cyber bystanders [15]. An article written by du Plessis et al. 2019, stated that cortisol has a role in the relationship between childhood trauma resulting from bullying. Figure 1 goes in-depth about the changes in brain and cognition that create cyberbullying and its impact. Peer victimization influences the structure of the ventrolateral prefrontal cortex, but is dependent on gender. Boys who were constantly bullied had higher cortisol secretion levels and less vIPFC (ventrolateral prefrontal complex), compared to those who were not frequently bullied. vIPFC controls emotion, reward, motivation, threat detection, and fear. Cortisol reduces things that would be nonessential or harmful in a fight-or-flight situation. A higher cortisol level can affect your mood subsequently making you more depressed. A study created by Quinlan showed that there were changes in the left putamen volume due to anxiety, peer victimization, and stress. The left putamen is responsible for reward processing, movement control, and learning [16].

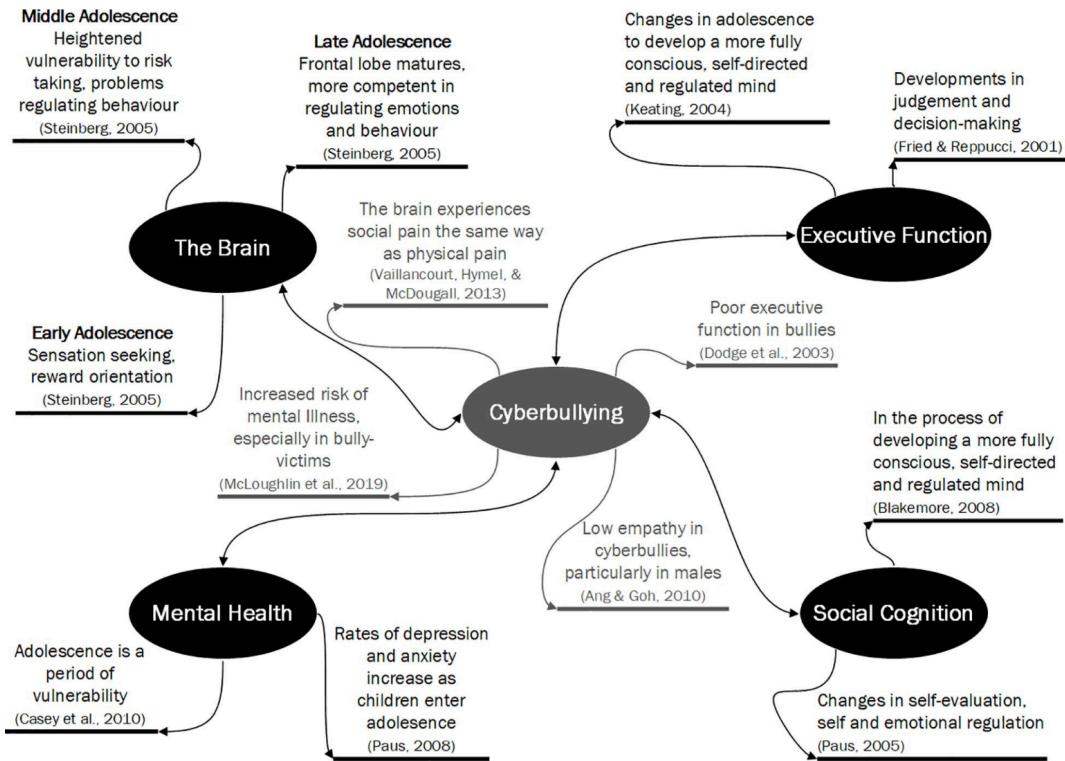


Figure 1 Alteration of the brain and cognition that influences cyberbullying (McLoughlin et al., 2020)[17]

A study conducted in Europe by Mcwen looked at the brain structure of victims who suffered from bullying and those who never experienced it. The group that was bullied had higher levels of anxiety compared to those who hadn't. There was brain adjustment displayed with the putamen and the caudate, these structural areas of the brain play a critical role in anxiety disorder. Chronic bullying victims also have white matter changes in the brain, making them vulnerable to depression. Victims of bullying have trouble grasping emotional cues and taking control of their emotions. These problems appeared because of the alterations of the emotional processing areas such as the amygdala and the prefrontal cortex. Chronic bullying can lead to the rise of stress hormones, like cortisol in areas compromising areas like the reward processing areas. These modifications can make you more reactive to stress and change your circuitry in the reward system, making you susceptible to developing uncontrolled addiction habits to substances. The release of these hormones can affect your immune system. The effects of bullying on the brain and mental health do not go unnoticed, the impact of these outcomes relies on several factors, such as the type of bullying, cultural circumstances, and personal coping mechanisms.

Limitations and Biases

A key question in this research is the extent of bullying because it can vary significantly across cultures. For instance, in some Asian countries, bullying can be more ruthless compared to the United States. Cultural differences, therefore, play a vital role in shaping the endurance of bullying. Equally important is how the individual manages the bullying, as this can influence the

long-term consequences. Evaluating these factors is crucial for understanding the full impact of bullying.

Additionally, children develop different coping mechanisms in response to bullying, with some adopting healthier strategies while others may resort to more harmful methods. This can result in more significant changes to the brain in children who develop unhealthy coping mechanisms, compared to those who participate in more positive ones. The child's family environment also plays a critical role in their brain development when exposed to bullying. For example, children who have experienced other forms of trauma may exhibit symptoms similar to those of bullying.

This research review does not focus solely on one type of bullying, which raises important questions. For instance, does one form of bullying have a more pronounced effect on the brain than another? Furthermore, we cannot fully assess the impact without knowing about the child's personal life, such as whether they live in a hostile environment or have access to therapy. Children who receive treatment such as therapy are less likely to experience severe long-term brain effects in adulthood compared to those who do not.

Conclusion

Bullying throughout childhood can cause neurotic changes as the victims progress into adulthood. These damages are linked to higher cortisol secretion levels, brain morphology, and mental illness. These changes affect cognitive functions making it harder to do things than the average person. Since chronic peer victimization can contribute to causing mental illness, it can correspond to physical illness. Limitations are currently throughout this study because of cultural differences and coping mechanisms.

References

- [1] National Center for Education Statistics. (2021). *Bullying*. Ed.gov; National Center for Education Statistics. <https://nces.ed.gov/fastfacts/display.asp?id=719>
- [2] U.S. Department of Health and Human Services. (2019). *What Is Bullying*. StopBullying.gov; U.S. Department of Health and Human Services. <https://www.stopbullying.gov/bullying/what-is-bullying>
- [3] Cleveland Clinic. (2022, May 23). *Cerebral Cortex*. Cleveland Clinic. <https://my.clevelandclinic.org/health/articles/23073-cerebral-cortex>
- [4] Guy-Evans, O. (2021, June 11). *Somatosensory Cortex Function and Location | Simply Psychology*. [Www.simplypsychology.org](https://www.simplypsychology.org/somatosensory-cortex.html).
- [5] Konrad, K., Firk, C., & Uhlhaas, P. J. (2013). Brain Development [10] Robinson, J. (2023, September 20). *How Does Mental Health Affect Physical Health*. WebMD. <https://www.webmd.com/mental-health/how-does-mental-health-affect-physical-health>
- [11] Garavan, H., Bartsch, H., Conway, K., Decastro, A., Goldstein, R. Z., Heeringa, S., Jernigan, T., Potter, A., Thompson, W., & Zahs, D. (2018). Recruiting the ABCD sample: Design considerations and procedures. *Developmental Cognitive Neuroscience*, 32, 16–22. <https://doi.org/10.1016/j.dcn.2018.04.004>
- [12] Brant-Zawadzki, M., Gillan, G. D., & Nitz, W. R. (1992). MP RAGE: a three-dimensional, Tr-weighted, gradient-echo sequence--initial experience in the brain. *Radiology*, 182(3), 769–775. <https://doi.org/10.1148/radiology.182.3.1535892>
- [13] Queensland Government. (2022, July 12). *Brain Map: Temporal Lobes | Queensland Health*. Qld.gov.au. https://www.health.qld.gov.au/abios/asp/btemporal_lobe
- [14] Bissière, S., Plachta, N., Hoyer, D., McAllister, K. H., Olpe,

-
- During Adolescence. *Deutsches Aerzteblatt Online*, 110(25), 425–431.
<https://doi.org/10.3238/arztebl.2013.0425>
- [6] Wolke, D. (2001). Bullying involvement in primary school and common health problems. *Archives of Disease in Childhood*, 85(3), 197–201. <https://doi.org/10.1136/adc.85.3.197>
- [7] Mayo Clinic. (2021, June 19). *Social Anxiety Disorder (social phobia) - Symptoms and Causes*. Mayo Clinic.
<https://www.mayoclinic.org/diseases-conditions/social-anxiety-disorder/symptoms-causes/syc-20353561>
- [8] Hysing, M., Askeland, K. G., La Greca, A. M., Solberg, M. E., Breivik, K., & Sivertsen, B. (2019). Bullying Involvement in Adolescence: Implications for Sleep, Mental Health, and Academic Outcomes. *Journal of Interpersonal Violence*, 36(17-18), 0886260519853409.
<https://doi.org/10.1177/0886260519853409>
- [9] Ehrenreich, S. E., & Underwood, M. K. (2016). Adolescents' internalizing symptoms as predictors of the content of their Facebook communication and responses received from peers. *Translational Issues in Psychological Science*, 2(3), 227–237. <https://doi.org/10.1037/tpsoooooo77>
- H.-R., Grace, A. A., & Cryan, J. F. (2008). The Rostral Anterior Cingulate Cortex Modulates the Efficiency of Amygdala-Dependent Fear Learning. *Biological Psychiatry*, 63(9), 821–831. <https://doi.org/10.1016/j.biopsych.2007.10.022>
- [15] Straub, J., Brown, R., Malejko, K., Bonenberger, M., Grön, G., Plener, P. L., & Abler, B. (2019). Adolescent depression and brain development: evidence from voxel-based morphometry. *Journal of Psychiatry & Neuroscience*, 44(4), 237–245.
<https://doi.org/10.1503/jpn.170233>
- [16] Ghandili, M., & Munakomi, S. (2020). *Neuroanatomy, Putamen*. PubMed; StatPearls Publishing.
<https://www.ncbi.nlm.nih.gov/books/NBK542170/>
- [17] McLoughlin, L. T., Lagopoulos, J., & Hermens, D. F. (2020). Cyberbullying and Adolescent Neurobiology. *Frontiers in Psychology*, 11. <https://doi.org/10.3389/fpsyg.2020.01511>

The impact of parenting styles on structural neuroplasticity in childhood and adolescence

Beverly Tadeo

Abstract

When raising a child, there are several factors to consider, one of which is how to raise them. Children are naturally curious and begin learning at a very early age, so it is important to understand the impact this can have. The environment a child is raised in can impact their neuroplasticity. The different parenting styles can be nurturing or neglectful, either of the parenting styles can hinder cognitive and emotional development. Data has shown that children raised in toxic or stressful environments may experience long-term effects on their brain structure and function, leading to cognitive and behavioral issues in adolescence and later on in adulthood. This paper looks into how different parenting styles can influence neuroplasticity and the importance of a healthy environment for brain development.

Neuroplasticity

Four major processes occur in the brain in order for neuroplasticity to function properly: angiogenesis, synaptogenesis, dendritic arborization and neurogenesis [1]. Angiogenesis is the formation of newly created blood vessels within the brain and its structures. Synaptogenesis is the creation of new synapses that are formed within the brain structures. Dendritic arborization is the growth of dendritic spines, growing as they gather more information. Neurogenesis is the growth of new cells in parts of the brain crucial for embryo development and can continue developing in certain brain regions after birth and through your lifespan. There are two main types of neuroplasticity, structural and functional. Structural neuroplasticity refers to the brain's ability to physically change after retaining knowledge. The physical structure in the brain forms more neurons and synaptic connections when a person learns or experiences something new. Functional neuroplasticity is the brain's ability to move functions from a damaged area to an undamaged area in the brain[2]. When someone is experiencing a brain injury the pre-existing neurons begin to die and synaptic connections are making new neurons to retrieve lost functions.

Infancy and adolescence are crucial time periods for the brain to develop. The first years of a child's life is when neurons rapidly develop and evolve. A child's brain starts to develop its structures and its ability to learn new things, enhancing their cognitive development. The brain rapidly develops and is about ninety percent developed by the age of five years old [2]. During this

rapid growth is when neuroplasticity is its strongest, being exposed to different situations or environments allows the brain to absorb new information and use it for long term memory. As a human ages, the ability of the brain to change decreases, meaning that it is important to learn things at an early age to effectively influence the neuroplasticity in the brain. Being exposed or introduced to certain environments can affect the brain's structure and their ability to grow and expand.

Parenting styles

Parenting styles can be harmful to the brain and its ability to form and enhance structural neuroplasticity. Research has shown scientific evidence that proves chronic stress in early childhood can be toxic and harmful to the developing brain [3]. The amygdala in particular is affected and is involved in processing emotions and stress. Stress and trauma can alter brain development, potentially leading to emotional and cognitive challenges later in life. There have been various studies that have shown the amygdala decreasing and having a smaller volume due to anxiety. However, studies were considered inconclusive because they failed to contribute other factors that could affect the outcome of the study and its negative effects. Changes that occur in the brain during a crucial time of brain development can cause disorders known as depression and anxiety in the future. Having no adult support allows toxic stress to build up and change the architecture of the brain. Parenting plays an important role in brain development and can affect structural plasticity, especially in early stages of brain development.

A child is first exposed to their parents and the environment created by their parents. Parents teach their kids language, habits, interactions, etc., everyone has their own way of parenting and according to psychologists Diana Baumrind, Eleanor Maccoby, and John Martin there are 4 main types of parenting styles. Authoritarian, authoritative and permissive and neglectful, are the four main parenting styles [4]. Authoritarian parenting is seen as a strict parenting style, enforcing rules and having high expectations for their children. Authoritative is the preferred or standard type of parenting, having a balanced and healthy relationship with each other. Permissive parenting has little to no expectations from the child, this parenting style is seen as a friend relationship rather than a parenting relationship. Neglectful parents are usually not involved in their children's life, minimal nurturing and emotional fulfillment. Parents may fall into one or more of these categories. Some of these parenting styles can lead to bigger issues in the future for these children.

Impact of parenting on brain

Neglect and authoritarian parenting styles can be harmful to the brain and its ability to form and enhance structural neuroplasticity. The brain develops and changes as the child goes through new experiences. Studies have found that children who experience social neglect in early years show reduced electrical activity in the brain, which hinders proper brain development. For example a sensitive area in the brain is the prefrontal cortex, an important part in your brain that contributes many functions in the brain like problem solving skills and memory. Studies on adolescents and adults who experienced extreme neglect during childhood showed smaller volumes in their

prefrontal cortex when compared to individuals who did not have serious neglect. Neglect and permissive parenting styles can put the child at risk for cognitive and behavioral disorders later on in adolescence or adulthood [5]. The impact that can be made on only a portion of your brain from trauma and stress is harmful and should be recognized. The scientific evidence provided proves that chronic stress in early childhood can be toxic and harmful to the developing brain. Having no support from parents allows toxic stress to build up and change the architecture of the brain.

There was a research study approved by the Institutional Review Committee of Konuk University using the PSS scale. Perceived Stress Scale (PSS) a self report questionnaire that measures stress levels [6]. The data showed that higher perceived stress was associated with decreased brain activity, specifically in regions like the prefrontal cortex, which plays a key role in decision-making and emotional regulation[7]. The PSS test score ranges from 0 to 40, high scores indicating a greater level of perceived stress. In the study, the moderate-stress group had a PSS score ranging from 15 to 18. There were a total of 37 participants in the moderate-stress group, 17 males, all 20-30 years old. The high-stress group had a total of 38 participants , 15 males and 23 females all 20 to 34 years old. Before initiating the test, participants were asked to maintain an average score of 95 on elementary arithmetic problems that were presented by difficulty over a time limit of 3 s. There were five stages to this study, The training phase, allowed participants time to adapt to the response button and solve problems. The rest phase was 90 s long and they were allowed to rest comfortably. The control phase 90 s, solved problems without any stress inducers. The stress task phase, they

solved problems under stress-inducing conditions. To induce acute stress 300 s, there was a visual of the time limit of 3 s. The participants were given feedback on the problem they just solved (correct, incorrect, or no response) for 2 s along with their mean score before moving on to the next question. 60 items were presented. The recovery phase (180 s) extracted brain signal changes when the participants were in a stable condition after performing all tasks. Functional MRI (fMRI) images were taken for all participants throughout the entire duration of the experiment. Below are the brain mapping images, The first figure is (a) moderate-stress and (b) high-stress groups during the stress-inducing condition. Figure two are the two groups (a) moderate-stress and (b)

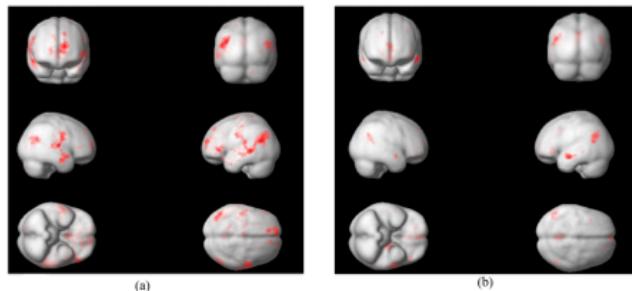


Figure #1. (a) moderate-stress and (b) high-stress groups during the stress-inducing conditions

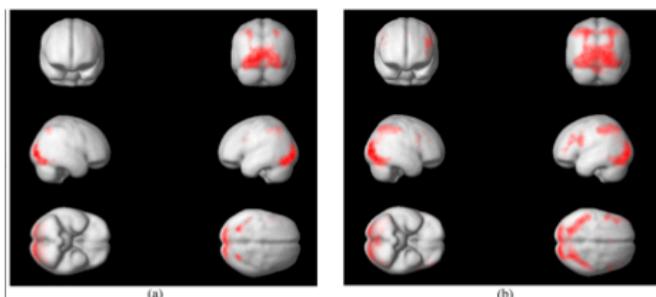


Figure #2. (a) moderate-stress and (b) high-stress group during the recovery state

high-stress group during the recovery state.

This study shows the impact of stress on the brain, participants who had high stress levels showed more activity in the brain during the recovery stage rather than having more activity during the stress inducing test they were given. The study proves how impactful environments can be on the brain. Structural neuroplasticity can not reach full potential if the brain is exposed to stressful or toxic environments created by parents.

Limitations/ Biases

There is still debate on whether or not authoritative parenting should be the standard parenting style. While it is seen as the standard, other parts of the world would disagree because of the difference of cultures. Authoritative parenting is mostly applied in Europe and America. Chinese and African American researchers say they view parenting as one of the best parenting styles because they “are defined as parents who care, control, and pay attention to children”. As Americans we view authoritarianism as strict and unreasonable at times but Chinese and African American researchers pointed out that it is not as bad as we make it sound [8]. They believe that there should be rules and reinforcements the children should follow because they should respect their parents. Culture is a key factor as well when considering how it affects children and their brain plasticity, because they are raised differently and are shown different customs.

A study was done on adolescents who have mental disorders and according to the results of the study, the adolescents perceived their parents as more authoritarian. The adolescents found that their habits came from their parents, their parents’ attitude led to increased self-judgment and aggression toward others. But another study made by Dwairy et al, eight Arab societies on adolescents found authoritarian parenting did not have a high impact and was not directly associated with higher psychological disorders. They found that authoritarian parenting by itself is not associated with negative outcomes. There are many opinions and evidence that are associated with this particular parenting style. There are different factors that contribute to Americans having more mental disorders with authoritarian parenting than other cultures. Parenting and the environment made by parents are important factors that will influence the brain and its structural plasticity. It is important to look at these studies and gather data from these findings to figure out a solution or an answer to this issue.

Conclusion

The neuroplasticity of the brain is sensitive to environmental factors, during critical periods of childhood and adolescence. The impact of stressful and traumatic environments has been found to be harmful to the brain and its plasticity. By understanding the role of parenting and its effects on neuroplasticity, there can be better support for children’s brain development and promote healthier and adaptive environments during growth. Parenting styles that could be harmful are, neglect, authoritarian and permissive. Each one of these parenting styles have their own flaws. It is either the lack of presence from the parents or controlling the child to the point the child has high stress levels.

Authoritative parenting is seen as one of the best parenting styles to fall into because of its balance. Having a healthy relationship with your kid can help increase cognitive development.

References

- [1] Innocenti, Giorgio.(2022). Defining Neuroplasticity. Handbook of Clinical Neurology. <https://www.sciencedirect.com/science/article/abs/pii/B078012810410200001>. Retrieved: 11/20/2024.
- [2] NCBI. (2021). *Neuroplasticity and Rehabilitation: From Mechanisms to Clinical Implications*. PMC.<https://pmc.ncbi.nlm.nih.gov/articles/PMC10741468/>. Retrieved: 11/10/2024
- [3] Kelley, Anisa. (03/02/2023). Brain Development in Early Childhood. Lurie Children's Blog. <https://www.luriechildrens.org/en/blog/early-childhood-brain-development-and-health/>. Retrieved: 11/15/2024.
- [4] Neuroskills.com. (n.d.). *How Neuroplasticity Works*. Neuroskills. Retrieved from <https://www.neuroskills.com/brain-injury/neuroplasticity/how-neuroplasticity-works/>. Retrieved: 11/19/2024.
- [5] NCBI Bookshelf. (2019). *Neuroplasticity and Recovery after Brain Injury*. In *Neuroplasticity: The Potential for Recovery*. Retrieved from <https://www.ncbi.nlm.nih.gov/books/NBK568743/>. Retrieved: 11/19/2024
- [6] Harvard University Center on the Developing Child. (2016). *InBrief: The Science of Early Childhood Development*. Harvard University. <https://developingchild.harvard.edu/resources/inbrief-science-of-ecd/>. Retrieved: 11/20/2024
- [7] ProQuest. (2023). *The Impact of Neuroplasticity on Child Development*. *Journal of Neuroscience and Child Development*, 34(5), 123-135. <https://www.proquest.com/docview/3120523104/7B4E8DE2765D4AACPQ/2?accountid=210620>. Retrieved: 11/20/2024.
- [8] Febiyanti, Anita.(2020). Is Authoritative Parenting the Best Parenting Style?. Advances in Social Science, Education and Humanities Research. <http://creativecommons.org/licenses/by-nc/4.0/>. Retrieved: 11/10/24
- [9] UC Davis Biotech. (2022). *The Role of Neuroplasticity in Healing*. UC Davis Biotech Blog. <https://biotech.ucdavis.edu/blog/neuroplasticity>. Retrieved: 11/10/2024

The effects of space exploration on the brain

Evelyn Gaspich

Abstract

There are many different effects of space exploration. Space is often considered the next frontier for exploration, the exploration of life in the universe, and understanding the creation of the universe. However, there are many dangers that most people need to be made aware of. Among these, the most prevalent issues are space radiation, isolation and confinement, and microgravity. The most dangerous issue of space travel is radiation due to its long-lasting potential effects from a short exposure time.

Background 1

Space radiation is not evenly spread out. Some places have thicker pockets of radiation and others have thinner radiation, and space radiation can depend on what type of celestial bodies are nearby, the Sun has a lot of radiation around it vs. a vacuum of "empty" space. Space radiation is made up of atoms whose electrons have been left behind due to the speed at which the protons of those atoms travel. There are three types of space radiation: solar particle events, the radiation inside Earth's magnetic field, and galactic cosmic radiation. Solar particle events occur when things like solar flares happen and send millions of gamma rays and X-rays, protons, and electrons into space. Fortunately, those on Earth are protected from the worst of these particles by Earth's magnetic field, which repels charged particles. However, some radiation gets trapped inside the Earth's atmosphere. The radiation that gets trapped is called ionizing radiation and is more threatening than non-ionizing radiation [1, 2].

Non-ionizing radiation comprises low-energy rays that are not typically harmful to humans, such as radio, microwaves, infrared, visible, and UV rays. Ionizing radiation comprises high-energy rays that are very difficult to shield from because it is much harder to shield against than non-ionizing radiation. Some examples of ionizing radiation include alpha and beta particles, gamma rays, and X-rays. Alpha particles are the nuclei of a helium atom, and beta particles are the electrons of the helium atom traveling near the speed of light [1].

The most dangerous type of radiation for space exploration is Galactic Cosmic Radiation (GCR) which is made up of the nuclei of all elements spanning Helium (which makes up 89% of GCR) to Uranium (only found in trace amounts). These nuclei travel at the speed of light and are very difficult to block because of their speed [2]. Astronauts that travel beyond Earth's low orbit (around 160-2,000 km) are exposed to radiation (50-2,000 mSv) the equivalent of 150-6,000 chest

x-rays (1 mSv is equivalent to 3 chest x-rays) [1]. While space radiation is the most troublesome problem concerning space travel, there are other concerns, such as microgravity.

Contrary to popular belief, no one has and never will experience true zero gravity because there are still trace amounts of gravity even in the middle of space. The researchers at the International Space Station (ISS) are in microgravity because they are going so fast around the Earth that they continuously fall towards it, causing them to float. Additionally, Earth's gravitational field is 250 miles above the surface, and at that 250th mile, the strength of gravity is 88.8% of that experienced at the surface [3]. There are many dangers associated with space travel, but one final consideration for space exploration is isolation and confinement.

There have been many missions where researchers are alone for months with little to no social contact. For example, Antarctic missions, the ISS, Mars Duna Alpha, CHAPEA, HERA, and countless more. Human beings evolved to be social, this is shown by the effects of COVID-19, with society essentially shutting down, and people staying in their homes with limited contact with each other. Putting crew members in situations where there is minimal contact with the rest of society, and only with a small group of people, can be detrimental to their mental health, and could cause them to be unable to complete their mission [4, 5]. The effects of space radiation, microgravity, and isolation and confinement are numerous and can have long-lasting, even permanent, effects.

Effects

Interestingly enough, even though radiation can cause cancer, it is also an option for cancer treatment. The radiation types used to treat brain cancer are protons, X-rays, and gamma rays [6]. Radiation can cause difficulties with learning, memory, processing speed, attention, cognitive flexibility, the ability to switch between tasks smoothly, and executive functions, as well as how we organize our thoughts. Radiation treatment also reduces the structural complexity of neurons, which causes the neuron to become less active, and send less and less information. A study that exposed mice to radiation found that there were more beta-amyloids, proteins that have been linked to the development of Alzheimer's, and dense fibrillar proteins, which build structures in cells and help build amino acids, in the cerebrum [7, 8].

A study done with mice that were exposed to a lower level of radiation and exposure to microgravity found that the mice developed weakened sensorimotor function, using vision, smell, touch, or other sensory inputs to kickstart a motor response, for example, catching a ball, motivation, and attention after 72 hours of exposure. Over 12 months, the mice showed a change in synaptic plasticity, the ability to strengthen or weaken the connections between neurons, hippocampal neurogenesis, the creation of new neurons in the hippocampus, and cognitive function, the ability to think and perceive the world. Learning and behavioral deficiencies were also observed [9].

In male mice, exposure to accelerated charged particles revealed impairments in cognitive learning and blood levels indicated a likelihood of later cognitive deficits. However, female mice

were more prone to hippocampal neurogenesis damage. This is also shown in human astronauts, with male astronauts more likely to develop neuro-ocular syndromes than women, although that could be because of a difference in body weight. Neuro-ocular syndrome occurs when the back of the eye is compressed, often leading to vision issues.

The changes in the brain brought about by space radiation have been shown to last for over a year, with no shown regeneration. The damaged areas and functions include the hippocampus, memory storage and formation, cortical neurons, sensory perception and decision-making, the prefrontal cortex, decision-making and reasoning, and the entorhinal cortex, memory, sensory processing, and spatial navigation. Some of these effects of space radiation are notable for their

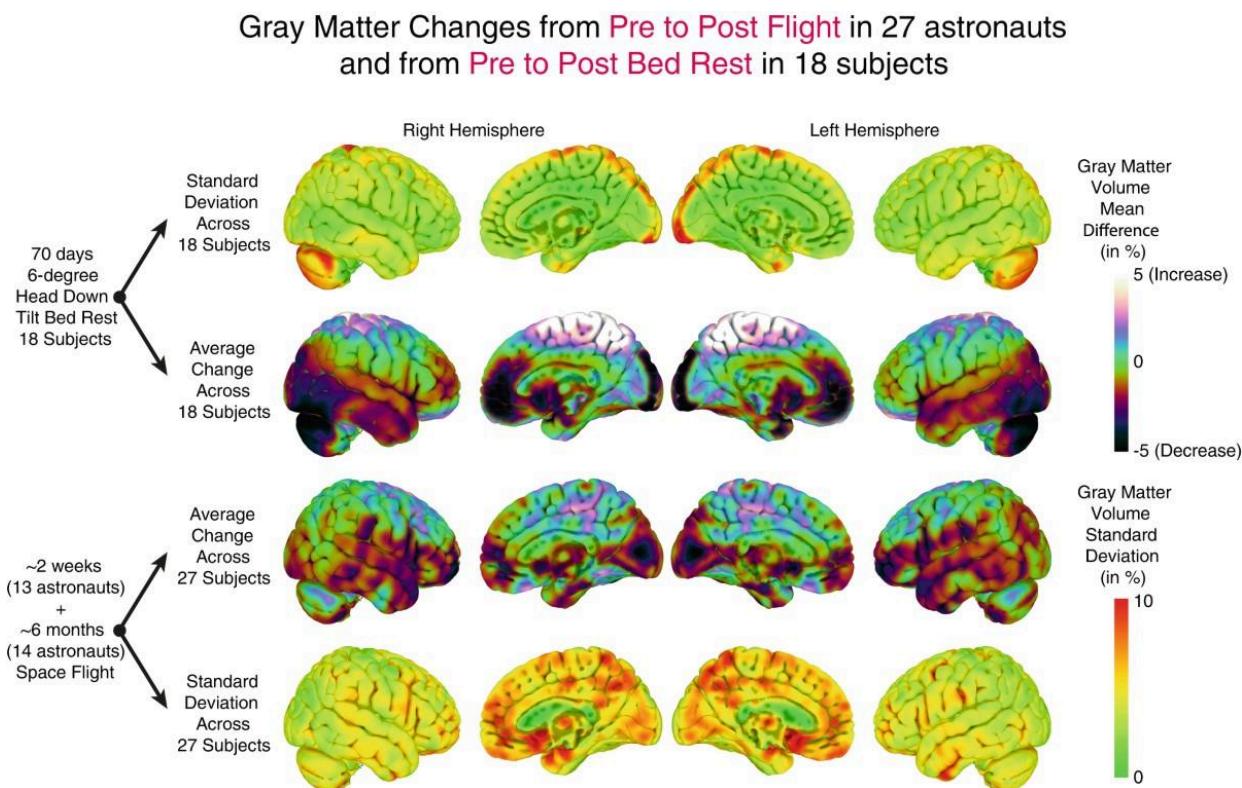


Figure 1. [15]

appearance in Alzheimer's, dementia, and premature brain aging. Space radiation can also change the structure of DNA, it can damage the Central Nervous System (CNS), and cause cancer, and both space radiation and microgravity can cause cardiovascular issues [9, 10, 11]. While space radiation is the most prevalent issue, there are other dangers to spaceflight, such as microgravity.

Microgravity has a different effect on the brain than space radiation, but it still causes negative effects. There are countless videos of astronauts drinking a floating bubble of water, caused by microgravity, but that means the fluid in the inner ears is also affected. The fluid in the inner ears is found in the cochlea and has important roles in hearing and balance. The cochlea is the spiral cavity in the ear that contains fluid and tiny hairs called stereocilia, feels the vibrations from the

liquid, and then sends electrical signals to the brain to be turned into sound. These tiny hairs are susceptible to damage if there are too many vibrations in the cochlea, and can lead to hearing loss.

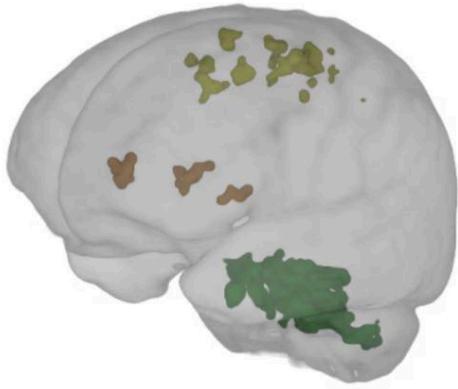
Microgravity affects spatial orientation, head-eye, and hand-eye coordination, and balance, and some experience space motion sickness [12, 13]. It can also cause vision issues like cataracts due to the tendency of fluids to move upwards and into the brain, which can lead to swelling, and the optic nerve and even the back of the eye can be compressed which is called neuro-ocular syndrome [14]. When astronauts return to gravity, that shift causes the fluids in the body to flow how they normally would on Earth. This sudden change can lead to post-flight orthostatic intolerance, the inability to control blood pressure, and can lead to lightheadedness and fainting. Motion sickness is also a common effect of damage to the vestibular system, and can lead to impairment in heart rate, blood pressure, and breathing patterns. Baroreceptor dysfunction can cause orthostatic imbalance, which

causes symptoms when standing up or sitting down. Baroreceptors are receptors that interpret physical stimuli, which then affect blood pressure [7].

The brain also shifts upward due to microgravity, as shown in Figure 1, and shows an increase in grey matter at the vertex and a decrease in grey matter at the lower cerebral cortex. The volume of perivascular space, fluid-filled cavities that cushion the blood vessels in the brain and spinal cord that regulate fluid exchange and waste, also increases after space flight and is typically seen in an aging brain and brains with neurological conditions [9].

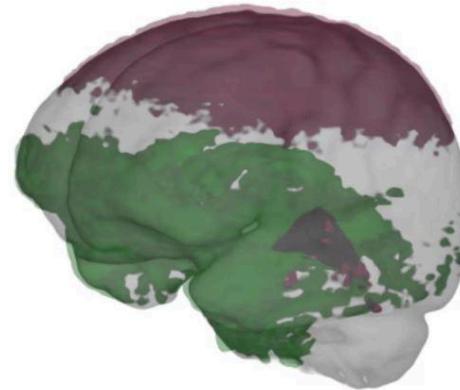
The body itself also goes under significant changes while in microgravity. Weight-bearing bones such as legs, spine, hips, etc., lose ~1-1.5% of mineral density per month of space flight [16]. Muscles are also at risk because they aren't being constantly used to combat the gravity on Earth, so they lose some of their mass. The heart is affected as well. On Earth, the heart can let gravity carry the blood to the lower extremities, and the organs that are above the heart, the brain for example, have stronger vessels and valves to go against gravity. In microgravity, that changes, because fluids tend to float upwards, so now the heart has to exert more force to send the blood to the lower extremities, which can lead to the heart becoming weakened [14, 13].

Microgravity can also affect cells at their anatomical level, affecting the placement of structures that help the cell function, in the cytoskeleton, and also affects DNA replication, and RNA and protein transcription. Overall, cell structures are more disorganized following exposure to microgravity [7]. Studies done on the brains of astronauts post-space flight found that there was significant intracranial fluid redistribution, with a cerebrospinal fluid (CSF) and free water reduction in the ventral frontal, temporal, and occipital lobes as shown in Figure 2.



Net brain tissue increases in three major motor areas after spaceflight: primary motor cortex (yellow), basal ganglia (orange), and cerebellum (green)

Illustrations by Steven Jilings and Ben Jeurissen (University of Antwerp) using MRtrix3 (www.mrtrix.org)



Spaceflight causes a volume redistribution of cerebrospinal fluid with less volume in upper (red) and more in lower parts of the brain (green)

Illustrations by Steven Jilings and Ben Jeurissen (University of Antwerp) using MRtrix3 (www.mrtrix.org)

Figure 2. Distribution of CSF fluid within the brain as an effect of microgravity [17]

Microgravity also increases the risk of developing venous thrombosis and blood clots in the neck [9]. All 12 astronauts involved in the study returned with a larger superior sagittal sinus (SSS) volume. The SSS is a large vein in the brain that runs between the two hemispheres and is responsible for returning deoxygenated blood from the brain to the heart [17]. If the volume of the SSS increases, then it causes an increase in intracranial pressure, venous congestion, slow blood flow, and blood clotting. A study on how the brain was affected by microgravity found an increase in connectivity in some areas of the brain and a decrease in connectivity between others. Some notable standouts are decreased connectivity in the thalamus, which acts as a relay station for sensory information. In the posterior cingulate cortex, whose function is undefined, with ideas that it controls the attention span, and there are other hypotheses that it controls the balance between external and internal thought [18]. There were also increases in the right angular gyrus, which is responsible for the interpretation of languages, and different parts of speaking and writing [19].

The immune system is also affected because of stress, radiation, microgravity, and altered nutrition. Proper nutrition is extremely hard to come by naturally due to the types of food that are sent/go with astronauts because they have to last for months, which leads to astronauts having to take a multitude of vitamins and mineral pills each day. Some aspects of the immune system can be weakened through infection, and some can become overactive, causing allergies, or hypersensitivity. There is also a possibility that certain viruses like chickenpox can be reactivated in microgravity due to the virus's dormancy in those who had chickenpox before and those who have received the weakened virus as a vaccine. It is suspected that stressful situations can cause the virus to awaken. A

study about virus reactivation was conducted by NASA and found that out of the astronauts that were tested, only 6 had mild symptoms [20, 14].

Isolation and confinement also profoundly affect astronauts' health. This greatly impacts their circadian rhythm because of the difference in dark/light cycles, the small and noisy environment, and the stress from isolation and confinement. Data from an Antarctic expedition showed a drastic change in the dentate gyrus, part of the hippocampus that helps form everyday memories, the volume associated with neurotrophins, proteins that manage the growth and survival of neurons, like brain-derived neurotrophic factor. Brain-derived neurotrophic factor is extremely important for learning and memory, acts as a neurotransmitter modulator, and plays an essential role in neuron growth and survival [21]. Overall, prolonged isolation and confinement can lead to problems with learning, memory formation, spatial navigation, problem-solving, emotional control, planning, and self-control. Another issue that was shown during the COVID-19 lockdown was a lack of sensory stimulation, a problem that is also shown in space. A study done on the psychological responses to the THOR simulation found that there was an increase in the level of social anxiety of the participants, which led to poorer quality of sleep, increased hostility, and decreased cognitive abilities [22].

Solutions

There are ways to prevent these effects, some of which are still being researched. Due to their low number of hydrocarbons, radiation from solar particle events, solar storms, or solar flares for example, or Earth's magnetic field can be shielded by water or polyethylene [10, 1, 11, 9]. Studies have also shown that if aspirin is taken after radiation, the risk for certain cancers can be decreased by up to 40% because of the anti-inflammatory effects [23]. More data on space radiation will be obtained from the Artemis mission.

The effects of microgravity are observed by conducting post-flight testing on balance and fine motor skills, then engineering solutions from the data obtained from these studies to improve the outcomes of those tests. Compression socks are also commonly used post-flight. MRIs are taken before and after flight to compare bone density and muscle mass post-flight. During spaceflight, self-fitness evaluations are constantly conducted, as well as resistive and aerobic exercises to minimize bone density and muscle mass loss, as well as to keep the heart healthy, and the mind sharp, improve mood, and improve balance and coordination [2, 16]. Additionally, neuro-ocular syndrome caused by spaceflight is corrected with surgery.

Currently, LED lights are being used in the ISS to set a more permanent sleep/wake cycle to prevent the effects of isolation and confinement [2]. Having things to do to pass the free time is also great for mental health. For example, former astronaut Nicole Scott brought art supplies into space to help pass the time. Journals are also a good tool to be able to vent frustrations without damaging the relationships between crewmembers. Additionally, meeting fellow crew members pre-flight can help to reduce the stress of being alone with new people for weeks. Another way that isolation and confinement are being mitigated is through the use of a space garden, which doubles in nutritional

and psychological benefits. Many astronauts enjoy taking care of the plants, some spending hours tending to them. Tending to the plants brought only positive feelings from the 7 astronauts in the study at the time [24].

In conclusion, there are many dangers to space exploration and habitation, including space radiation, microgravity, and isolation and confinement. Each of these dangers comes with its effects, such as markers for Alzheimer's, neurological disorders, impaired cognition, and behavioral disorders. However, researchers are moving towards solutions to lessen the negative effects of space exploration on the human brain.

References

- [1] NASA. (13/4/2017). Why Space Radiation Matters. NASA. Page 1, <https://www.nasa.gov/missions/analog-field-testing/why-space-radiation-matters/>. Retrieved: 10/29/2024.
- [2] Cranford, Nathan and Turner, Jennifer. (2/2/2021). The human body in space. NASA. Page 1, <https://www.nasa.gov/humans-in-space/the-human-body-in-space/>. Retrieved: 10/29/2024.
- [3] NASA. Hazard: Gravity Fields. NASA. Page 1, <https://www.nasa.gov/hrp/hazard-gravity-fields/>. Retrieved: 10/29/2024.
- [4] Jordan, Giles and Williams, Tom. (17/8/2018). Houston We Have a Podcast- Episode 58 (Hazard 2: Isolation). NASA. Page 1, <https://www.nasa.gov/podcasts/houston-we-have-a-podcast/hazard-2-isolation/>. Retrieved: 10/29/2024.
- [5] Choukér, Alexander and Stahn, Alexander C. (2020). COVID-19—The largest isolation study in history: the value of shared learnings from spaceflight analogs. Npj Microgravity. Page 1, <https://doi.org/10.1038/s41526-020-00122-8>. Retrieved: 10/23/2024.
- [6] Radiology (ACR). (30/9/2024). Brain Tumor Treatment. Radiologyinfo.org. Page 1, <https://www.radiologyinfo.org/en/info/thera-brain>. Retrieved: 11/4/2024.
- [7] Jandial, Rahul et al. (2024). Space-brain: The negative effects of space exposure on the central nervous system. Proquest.com. Pages 1,2, and 5, <https://www.proquest.com/docview/2102346364/fulltext/F634622ECD804BADPQ/1?accountid=210630&sourcetype=Scholarly%20Journals>. Retrieved: 11/12/2024.
- [8] Mouse Genome Informatics. (2024). dense fibrillar component Gene Ontology Term (GO:0001651). Jax.org. Page 1, https://www.informatics.jax.org/vocab/gene_ontology/GO:0001651. Retrieved: 11/20/2024.
- [9] Seidler, Racheal D et al. (2024). Effects of spaceflight on the brain. Proquest. Pages 1, 2, 3, 5, <https://www.proquest.com/docview/3082121661/A378CF5650EC4CC3PQ/2?accountid=210630&sourcetype=Scholarly%20Journals>. Retrieved: 10/29/2024.
- [10] NASA. (11/3/2024). About the Space Radiation Element. NASA. Page 1, <https://www.nasa.gov/reference/about-the-space-radiation-element/>. Retrieved: 10/29/2024.
- [11] NASA. (16/8/2017). NASA Protects Its Superheroes From Space Weather. NASA Protects Its Superheros from Space Weather. Page 1, <https://www.nasa.gov/humans-in-space/nasa-protects-its-superheroes-from-space-weather/>. Retrieved: 10/29/2024.
- [12] Arshad, Iqra and Ferré, Elisa Raffaella. (2022). Cognition in zero gravity: Effects of non-terrestrial gravity on human behaviour. Quarterly Journal of Experimental Psychology. Page 1, <https://doi.org/10.1177/17470218221113935>. Retrieved: 11/1/2024.
- [13] Jordan, Giles and Norsk, Peter. (31/8/2018). Hazard 4: Gravity. Houston We Have a Podcast- Episode 60 (Hazard 4: Gravity) NASA. Page 1, <https://www.nasa.gov/podcasts/houston-we-have-a-podcast/hazard-4-gravity/>. Retrieved: 10/29/2024.
- [14] NASA. (3/3/2021). Step 2, Station: Space Laboratory as Testbed for Moon, Mars. NASA Page 1, <https://www.nasa.gov/humans-in-space/step-2-station-space-laboratory-as-testbed-for-moon-mars/>. Retrieved: 10/29/2024.
- [15] Koppelmans, Vincent et al. (2016). Brain structural plasticity with spaceflight. Npj Microgravity. Page 1, <https://doi.org/10.1038/s41526-016-0001-9>. Retrieved: 11/11/2024.
- [16] NASA. (17/5/2021). Astronauts' Spines Under Scrutiny. NASA. Page 1, <https://www.nasa.gov/missions/station/astronauts-spines-under-scrutiny/>. Retrieved: 10/29/2024
- [17] Sample, Ian. (4/9/2020). Scans reveal how brain adapts to life in space. The Guardian. Page 1, <https://www.theguardian.com/science/2020/sep/04/scans-reveal-how-brain-adapts-to-life-in-space>. Retrieved: 11/7/2024.
- [18] Leech, Robert and Sharp, David J. (2013). The role of the posterior cingulate cortex in cognition and disease. Oxford Academic. Page 1, <https://doi.org/10.1093/brain/awt162>. Retrieved: 12/15/2024.
- [19] Jillings, Steven et al. (2024). Prolonged microgravity induces reversible and persistent changes on the human cerebral connectivity. Proquest. Pages 1, 2,

-
- <https://www.proquest.com/docview/2765249954/F15EC149CA3B403DPQ/2?accountid=210630&sourcetype=Scholarly%20Journals>. Retrieved: 10/29/2024.
- [20] NASA. (21/3/2019). NASA Investigates How Dormant Viruses Behave During Spaceflight. NASA. Page 1, <https://www.nasa.gov/humans-in-space/nasa-investigates-how-dormant-viruses-behave-during-spaceflight/>. Retrieved: 12/15/2024
- [21] Miranda, Magdalena et al. (2019). Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. *Frontiers in Cellular Neuroscience*. Page 1, <https://doi.org/10.3389/fncel.2019.00363>. Retrieved: 12/15/2024
- [22] Malpica, Diego et al. (2024). Investigating the psychological and physiological responses to isolation and confinement using the THOR space analog simulation. Proquest. Page 1, <https://www.proquest.com/docview/3073173165/57904DF13DBB4AFoPQ/4?accountid=210630&sourcetype=Scholarly%20Journals>. Retrieved: 10/29/2024.
- [23] Weeks, Jason et al. (24/1/2020). Space Radiation. NASA. Page 1,
- <https://www.nasa.gov/podcasts/houston-we-have-a-podcast/space-radiation/>. Retrieved: 10/29/2024.
- [24] NASA. (13/5/2021). Can Space Gardening Help Astronauts Cope With Isolation?. NASA. Page 1, <https://www.nasa.gov/humans-in-space/can-space-gardening-help-astronauts-cope-with-isolation/>. Retrieved: 10/29/2024.
- [25] Patel, Zarana Jordan, Giles. (10/8/2018). Hazard 1: Radiation. Houston We Have a Podcast- Episode 57 (Hazard 1: Radiation). Page 1, <https://www.nasa.gov/podcasts/houston-we-have-a-podcast/hazard-1-radiation/>. Retrieved: 10/29/2024.
- [26] Te Awamutu Space Centre (2024). What is zero gravity? Spacecentre.nz. Page 1, <https://www.spacecentre.nz/resources/faq/physics/zero-gravity.html>. Retrieved: 11/14/2024.

Media-Driven Beauty Standards: The Impact on Consumer Behavior, Body Image, and Mental Health

Mariangel Cisneros

Introduction

The ideal of beauty, as propagated through the channels of mass media, exerts a profound influence on the consumer's behavior, shaping the consumer's perception of one's body and self-esteem. Often these ideals are also put forward in flawless forms and unattainable standards, further pushed through advertising, social media platforms and popular cultures to yield narrow and unrealistic definitions of beauty. This has led many people, particularly women, to buy beauty products or undergo cosmetic procedures to try to meet these societal expectations. The continuous exposure to such media-driven ideals creates a vicious circle: people dissatisfied with their personal appearance become intricately tied to one's perceived value and social acceptance. Understanding how these media portrayals shape individual perceptions, behaviors, and broader cultural norms is key in addressing the harmful effects of beauty standards.

The Impact of Media Beauty Standards on Consumer Behavior and Feminine Consumerism

Media-driven beauty standards have a significant influence on feminine consumerism, shaping how women perceive their attractiveness and affecting their purchasing behavior. Recent research highlights the powerful role that media-imposed beauty ideals play in driving consumer decisions, particularly in beauty and self-care industries. Media outlets, including social media platforms, frequently promote narrow, idealized beauty standards—featuring flawless models with specific body types and facial features. These portrayals are not merely cultural expressions, but strategic marketing tools designed to sell products.

The dissatisfaction theory, rooted in neuroscience, explains how exposure to these unrealistic standards can trigger feelings of inadequacy and self-doubt in women. Brain responses to these media images often lead to negative self-perceptions, which, in turn, increase the desire to purchase products that promise to help meet these ideals. This creates a cycle where women are

continuously encouraged to buy beauty products and services in an attempt to attain the unattainable.

Examples of this can be seen in global beauty campaigns like Dove's "Real Beauty" (Dove, 2019) and the rise of Instagram influencers who promote cosmetic products (Pertus, 2024). Despite Dove's push for body diversity, many beauty campaigns still emphasize a narrow definition of beauty. Social media platforms like Instagram also play a key role, where influencers often promote beauty products and treatments that are presented as solutions to perceived imperfections. These strategies reinforce the idea that beauty is a commodity that can be purchased, further shaping consumer behavior.

The Role of Media and Its Effects on Body Image

Media portrayals of beauty often emphasize unrealistic ideals, featuring slender bodies, clear skin, and specific facial features. The pressure to conform to these standards is intensified by social media platforms like Instagram and TikTok, where influencers post edited or enhanced images of their bodies, contributing to a skewed perception of beauty.^{buch}

A prominent example of how media perpetuates unattainable standards is the rise of "fitspiration" content, which promotes a certain "ideal" body shape and lifestyle. This content typically emphasizes a tone, slim, yet muscular physique with a focus on fitness and diet, creating a narrow definition of health and beauty. Women who engage with "fitspiration" often report higher levels of body dissatisfaction and are more likely to engage in unhealthy behaviors to meet these ideals (Fardouly et al., 2018). These images foster comparison, prompting many women to purchase products that promise to help them achieve the "perfect" body. Such consumer behavior is driven not just by personal preference but by the constant reinforcement from the media that a woman's worth is tied to her appearance. Advertisements for beauty products, often promoting unattainable standards, play into these insecurities.

The media's portrayal of beauty ideals is widespread across industries like cosmetics, fashion, fitness, and wellness products. The beauty industry thrives on promoting narrow ideals, continually marketing products designed to enhance or correct a woman's appearance. In 2021, Americans spent an average of \$211.82 per consumer on beauty products, an increase from previous years, showing the rising importance of appearance in consumer spending (Demand Sage, 2023). This market-driven portrayal significantly influences consumer behavior, leading women to spend billions annually on beauty products and services that promise to help them meet these "ideal" images.

Additionally, the concept of the *Golden Facial Ratio* further compounds these standards. This ratio, which measures facial symmetry and proportionality, is often used in beauty assessments, with ideal facial features—including the proportion of the eyes, nose, and lips to the overall face—becoming benchmarks in media portrayals (M Cosmetic Surgery, 2023). This idea reinforces

the belief that beauty can be measured and quantified, further influencing both self-perception and consumer spending.

Different age groups may be affected differently by these media-driven ideals. Young women, in particular, are more likely to be influenced by social media and beauty trends, with adolescent and college-aged women spending more on beauty products and services compared to older age groups (Ballard Brief, 2023). This demographic is especially vulnerable to the impact of media portrayals of beauty, as their sense of self-worth can be more easily shaped by external influences.

Media-driven beauty standards create a direct link to feminine consumerism, where women's purchasing behaviors are shaped by the desire to conform to these ideals, often leading them to buy products that promise to help them achieve a particular look or body type.

Feminine Consumerism: Buying Into Beauty Ideals

The connection between media-driven beauty standards and consumerism is deeply embedded in the marketing strategies used by beauty and fashion companies. These industries capitalize on women's insecurities by positioning their products as essential tools for achieving the ideal beauty standards. Ads for makeup, skincare, and weight loss products often feature unattainable images of beauty, presenting women with a clear message: in order to be attractive or worthy, they must meet these ideals. As a result, billions of dollars are spent annually on beauty products, cosmetic procedures, and services like weight loss programs, all of which promise to help women achieve these standards.

This drive for conformity is not just about meeting physical beauty standards but is also tied to the concept of "convenience in conformity." As discussed in *The New York Times* (2018), convenience often comes with the expectation of conformity, where individuals are subtly pressured into following societal norms in exchange for ease and simplicity. In the context of feminine consumerism, convenience means easy access to products that promise quick results in conforming to these beauty ideals. Brands like Temu, Shein, and Fashion Nova have mastered this by offering fast fashion and beauty products that allow consumers to quickly follow trends and achieve the "ideal" look. These corporations thrive on offering affordable, mass-produced goods, appealing to consumers seeking convenience in meeting societal expectations (Deighton, 2023).

Shein has revolutionized the fast fashion industry by providing inexpensive, trendy clothing that aligns with ever-changing beauty and fashion standards. Through their rapid supply chain and data-driven business model, Shein and similar brands are able to produce and distribute products that reflect current beauty ideals, fueling a cycle of consumption. Temu, another rising player in the fast fashion world, has quickly gained traction by offering a vast selection of inexpensive products, making it easy for consumers to purchase items that promise to help them meet the media's definition of beauty and style. These companies, by capitalizing on the desire for both convenience and conformity, contribute to the reinforcement of narrow beauty standards, encouraging women to

buy into the idea that their appearance can—and should—be continually updated to align with the latest trends (Deighton, 2023).

This constant cycle of consumption and the pressure to conform to idealized beauty standards not only influence consumer behavior but also contribute to deeper psychological issues, such as body dysmorphia, where individuals struggle with distorted perceptions of their own bodies. Understanding the neuroscience behind these conditions sheds light on how media-driven beauty ideals can lead to lasting emotional and cognitive effects.

The Neuroscience of Body Dysmorphia

The media's portrayal of beauty standards plays a significant role in the development of body dysmorphia, particularly influencing how individuals perceive their bodies. Body dysmorphia is a complex mental health condition characterized by a distorted self-image, where individuals become preoccupied with perceived flaws that others often do not notice or deem insignificant. These preoccupations can lead to excessive behaviors such as mirror checking, skin picking, or comparing one's appearance to others in an attempt to "fix" imagined imperfections.

While body dysmorphia is primarily influenced by societal beauty ideals, the condition has a substantial neurological component that makes it particularly difficult to treat. Research has revealed that brain activity in individuals with body dysmorphia differs from typical patterns, particularly in areas responsible for self-reflection, visual processing, and self-evaluation. For example, studies show altered blood flow in the occipital lobe (responsible for visual processing) and the prefrontal cortex (involved in self-reflection and decision-making), both of which may lead individuals to misinterpret visual information about their appearance (Huff & Prasanna Tadi, 2023). This neurological misprocessing results in a distorted perception of one's body, where individuals might see themselves as overweight, underweight, or unattractive, even when these features are normal or idealized according to societal standards.

One of the key findings in neuroscience research is how individuals with body dysmorphia process reflective images differently from static photographs. When looking into a mirror, the brain processes live, dynamic images, which often leads to a more exaggerated, distorted self-perception compared to the more objective view provided by photographs (Dr. Jeffrey DeSarbo, 2021). This dynamic visual feedback can trigger negative emotional responses and reinforce a distorted self-image, creating a cycle of obsession and compulsive behaviors. For example, individuals with anorexia may perceive themselves as overweight despite being severely underweight, or someone with body dysmorphia may fixate on small, unnoticeable features like a mole or the shape of their nose (Fisher et al., n.d.). These responses highlight how the brain's processing of sensory input, particularly visual cues related to one's body, can become misaligned with reality.

The misperception of one's body in body dysmorphia shares similarities with delusional thinking, a phenomenon in which an individual's perception of reality becomes distorted. In this case, individuals with body dysmorphia often cannot perceive their bodies objectively, despite evidence to the contrary. This distorted view of themselves is not a result of vanity or mere

dissatisfaction, but rather a neurological misinterpretation of sensory input, which leads to significant psychological distress and daily impairments. Delusional thinking in body dysmorphia manifests as a persistent belief in perceived flaws, making it difficult for individuals to reconcile their distorted self-image with reality (DeSarbo, 2021).

Body dysmorphia is often comorbid with other mental health conditions such as depression, anxiety, and obsessive-compulsive disorder (OCD), further complicating its diagnosis and treatment. The psychological distress caused by the inability to reconcile one's self-image with reality can lead to severe emotional and social consequences, including isolation, low self-esteem, and a diminished quality of life. Compulsive behaviors like mirror checking can become all-consuming, impacting relationships, work, and overall well-being. The combined psychological distress and neurological misprocessing make body dysmorphia a particularly insidious disorder, where the brain's distorted interpretation of sensory input reinforces negative thought patterns.

Understanding body dysmorphia requires an interdisciplinary approach that integrates both psychological and neurological perspectives. Current treatments, such as cognitive behavioral therapy (CBT) and medication, aim to address the psychological symptoms by helping individuals challenge negative thought patterns and behaviors. However, the neurological underpinnings of the disorder suggest that future treatments may need to include neuroimaging or brain modulation techniques to better address the misprocessing of sensory input.

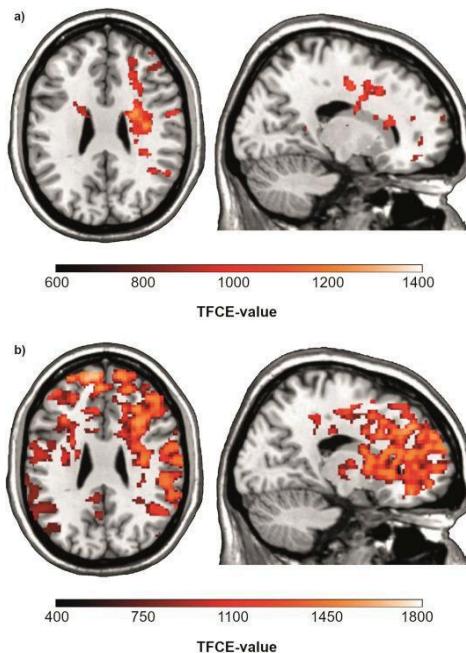


Figure 1. Brain Functional Correlates of Emotional Face Processing in Body Dysmorphic Disorder (Borgers et al., 2022).

This insight has led to the exploration of treatments that might directly target these neural pathways, such as neurofeedback or other brain-based interventions. Additionally, research into the

genetics of body dysmorphia is ongoing, with the hope of identifying biological markers that could help in both diagnosis and treatment (Feusner et al., 2016).

Anxiety and Depression Due to Beauty Standards and Body Image

Beyond body dysmorphia, media-driven beauty standards contribute significantly to heightened levels of anxiety and depression, particularly in individuals who internalize these ideals. Exposure to idealized images in the media often leads to feelings of inadequacy, self-loathing, and anxiety, especially among women. Studies indicate that the symptoms of anxiety can quickly escalate into more severe mental health conditions, such as clinical depression and generalized anxiety disorder ((National Institute of Mental Health, 2024)). This is particularly evident among women who are constantly exposed to media content that reinforces the notion that physical appearance is paramount. The constant pressure to meet these beauty standards creates a chronic state of distress, leading to mental health issues that extend beyond simple body dissatisfaction.

This distress is often further exacerbated by eating disorders, such as anorexia nervosa and bulimia. These conditions are commonly diagnosed in individuals who struggle with anxiety and depression, illustrating the complex relationship between body image and mental health. Those with eating disorders do not only battle distorted body images but also experience profound emotional distress, which intensifies their psychological struggles. The intersection of body dissatisfaction, eating disorders, and broader mental health challenges underscores the damaging impact that media-driven beauty standards can have on women's psychological well-being (Murnen et al., 2018). The constant cycle of striving to meet these unrealistic ideals often leads to unhealthy coping mechanisms, including disordered eating behaviors, further fueling the psychological burdens these women face.

Research consistently shows that body dissatisfaction is strongly correlated with the onset of anxiety and depression, particularly in individuals who feel disconnected from societal beauty standards. As women engage with media content that reinforces these ideals, they frequently internalize these standards, leading to higher rates of dissatisfaction and emotional distress. This internalization process is particularly harmful for young women, who are still in the process of developing their sense of self-worth and identity. The growing psychological burden created by these unrealistic beauty standards has profound consequences, contributing to the rise in anxiety, depression, and eating disorders.

In recent years, body positivity movements have aimed to challenge and dismantle these narrow beauty ideals, promoting acceptance of diverse body types and appearances. While these movements have made significant strides in encouraging self-love and acceptance, the pervasive influence of media-driven beauty standards continues to make it difficult for many individuals to fully embrace their natural appearance. Despite the positive changes brought about by body positivity, the mental health consequences of unrealistic beauty standards remain deeply entrenched in society (Cohen et al., 2020).

Conclusion

The media's relentless promotion of unrealistic beauty standards plays a key role in shaping consumer behavior, particularly by driving individuals to invest in products and services that promise to help them attain these narrow ideals. These portrayals not only influence purchasing decisions but also contribute to a wide range of psychological issues, such as body dysmorphia, anxiety, depression and low self-esteem. The pressure to meet these beauty standards creates a cycle of insecurity, where many women feel that their worth is determined by their physical appearance and the ability to meet these ideals. This constant starving for unattainable beauty fuels a consumer-driven culture where self-worth is often tied to external validation. Challenging these harmful media narratives and promoting a more diverse and authentic understanding of beauty can help break this cycle and encourage a healthier, more inclusive definition of self-worth. By addressing the psychological and societal impacts of beauty standards, we can move towards fostering a culture where value is based on individuality and authenticity, rather than superficial ideals of appearance and conformity. Only then can we begin to dismantle the damaging effects of these standards on mental health and well-being.

References:

- [1] Dove.(2019). Dove Campaigns. Dove UK. <https://www.dove.com/uk/stories/campaigns.html>. Retrieved: 12/10/2024
- [2] Pertus, Alexander. (29/09/2024). The Role of Influencers in Shaping Cosmetic Trends: A Double-Edged Sword. *ReportLinker*. Retrieved from: <https://www.reportlinker.com/article/8175>. Retrieved: 11/20/2024
- [3] Fardouly, Jasmine et al. (2018). Instagram Use and Young Women's Body Image Concerns and Self-Objectification: Testing Mediational Pathways. *New Media & Society*, 20(4), 1380–1395. Retrieved from: <https://doi.org/10.1177/146144817694409> Retrieved: 11/15/2024
- [4] Kumar,Naveen. (07/11/2024). 31 Beauty Industry Statistics 2024 - Trends & Insights. Retrieved from DemandSage. Retrieved from: <https://www.demandsage.com/beauty-industry-statistics/> Retrieved: 12/10/2024
- [5] Surgery, M. C. (16/06/2022). What is the Golden Ratio of Facial Aesthetics? Retrieved from Maningas Cosmetic Surgery. Retrieved from: <https://mcosmeticsurgery.com/what-is-the-golden-ratio-of-facial-aesthetics/>. Retrieved: 12/10/2024
- [6] Wu, Tim. (16/02/2018). The Tyranny of Convenience. *The New York Times*. Retrieved from: <https://www.nytimes.com/2018/02/16/opinion/sunday/tyranny-convenience.html> Retrieved: 12/05/2024
- [7] Deighton, John. (25/04/2023). How SHEIN and Temu Conquered Fast Fashion—and Forged a New Business Model. Retrieved from Harvard Business School. Retrieved from: <https://www.library.hbs.edu/working-knowledge/how-shein-and-temu-conquered-fast-fashion-and-forged-a-new-business-model> Retrieved: 12/01/2024
- [8] DeSarbo, Jeffrey. (2021). NeuroSeries 8: Neurobiology of Body Image. In YouTube. Retrieved from: <https://www.youtube.com/watch?v=rod4Utt7Qpc> Retrieved: 11/18/2024
- [9] Buchanan, Ben.(01/01/2011). Body dysmorphic disorder: a review of nosology, cognition and neurobiology. *Neuropsychiatry*, 1(1), 71–80. Retrieved from: <https://www.jneuropsychiatry.org/peer-review/body-dysmorphic-disorder-a-review-of-nosology-cognition-and-neurobiology-neuropsychiatry.pdf> Retrieved: 12/03/2024

-
- |11|Borgers, Tiana et al. (2022). Brain functional correlates of emotional face processing in body dysmorphic disorder. *Journal of Psychiatric Research*, 147, 103–110. Retrieved from:
<https://doi.org/10.1016/j.jpsychires.2022.01.007> Retrieved:
11/01/2024
- |12|Cohen, Rachel et al. (2020). The case for body positivity on social media: Perspectives on current advances and future directions. *Journal of Health Psychology*, 26(13), 2365–2373. Retrieved from:
<https://doi.org/10.1177/1359105320912450> Retrieved: 10/29/2024
- |13|Fisher, Eva et al. *Body dysmorphic disorder is more common than eating disorders like anorexia and bulimia, yet few people are aware of its dangers*. The Conversation. Retrieved from:
<https://theconversation.com/body-dysmorphic-disorder-is-more-common-than-eating-disorders-like-anorexia-and-bulimia-yet-few-people-are-aware-of-its-dangers-10558> Retrieved:
10/29/2024
- |14|National Institute of Mental Health. (April, 2024). *Anxiety disorders*. National Institute of Mental Health. Retrieved from:
<https://www.nimh.nih.gov/health/topics/anxiety-disorders>
Retrieved: 11/19/2024
- |16|Huff, Trevor et al. (2023). *Neuroanatomy, Visual Cortex*. Nih.gov; StatPearls Publishing. Retrieved from:
<https://www.ncbi.nlm.nih.gov/books/NBK482504> Retrieved:
10/24/2024

Is there increased hippocampal function in individuals who practice Abrahamic religions?

Chastity Spencer-Thomas

Abstract

The hippocampus is known for regulating memory, emotional processing, and spatial navigation (social behavior in this context), which plays a significant role in spirituality, moral reasoning, and decision-making. Neurotheology is the study of religious and spiritual experiences from a neurological perspective, providing evidence that meditation and intense prayer can combat hippocampal atrophy and enhance emotional stability. Specific examples include glossolalia in Christians, which alters CBF, and intense prayer in devout Muslims, which shifts activity in the anterior cingulate gyrus and frontal lobe. Secular communal gatherings & connections of religious practices to the building of social bonds and emotional well-being will be additionally assessed. Findings suggest that religious activities stimulate hippocampal function by enhancing the development of social bonds and emotional well-being. The challenges faced are the limitations in current research, including cultural biases and methodological inconsistencies, emphasizing the need for broader investigations into non-religious contexts. By bridging spirituality and science, this aids in gaining a deeper understanding of the brain's adaptability and capacity for connection. Delving into the relationship between the functions of the hippocampus and religious practices assist in determining whether or not spiritual activities positively alter brain activity.

Normal Function(s) of Hippocampus

The hippocampus is located in the temporal lobe of the brain, fixed right above each ear. It is responsible for storing explicit memories (allows one to consciously recall memories and facts), and transferring short-term memory to long-term storage. Its other functions include spatial navigation and processing declarative memory (any memory that can be described verbally). The hippocampal formation is part of the limbic system, and comprises the hippocampus proper, dentate gyrus (DG), & the subiculum. The hippocampus is a paired archicortical (3 layered) structure intimately linked to the limbic system and the six-layered neocortex. [i] These functions help understand how brain activity is connected to religious social gatherings, including individuals who are peer-influenced.

Hippocampus Activity in Groups

Functional neuroimaging studies conducted on hippocampus activity in social groups have shown the prefrontal cortex is heavily involved in moral reasoning, social conduct, experiencing and recognition of social & emotional decision-making. They “promote resilience and buffer negative neural consequences of stimuli” [1], assigning value to mental representation, social & emotional decision-making. The cingulate is involved in reward processing and emotional memory by sending and elaborating information passed between the hippocampal system and neocortical association areas [2]. The neocortical association areas include the somatosensory association cortex, visual association area, and premotor cortex. The hippocampus’s activity within social groups shows how the brain adapts to group dynamics, moral reasoning, and emotional decision-making.

Neuroscience of Religion

Neurotheology, also known as “spiritual neuroscience”, is “the neurological study of religious and spiritual experiences, focusing on the relationship between brain function and various mental states” [3]. The most common practice in the field of research is meditation. This is known for fighting hippocampal atrophy, the loss of hippocampal volume, a result of aging. Hippocampal atrophy can lead to impaired memory and amnestic syndrome, a critical symptom in Alzheimer’s disease [4]. Gray matter is brain tissue composed of neuronal cell bodies, synapses, & dendrites, associated with greater thinking skills and memory. Hippocampal atrophy negatively affects gray matter, leading to impaired memory and attention [5]. A study was held by Eileen Luders consisting of twenty-two individuals with more than five years of meditative experience who were paired with twenty-two controls to determine whether or not there would be an increase in gray matter in their brains compared to control participants. The results revealed via MRI a vast increase in gray matter in the right hippocampus, which is linked with the meditators being able to “cultivate positive emotions, retain emotional stability, and engage in mindful behavior” [3]. Meditating in Abrahamic religions like Islam and Christianity is to remember and connect with their gods. For Islam, the meditative type practiced is Dhikr and Salat. Dhikr is a form of Islamic worship in which one prays repetitively in order to remember Allah, the Islamic god. Salat is the second of the 5 pillars of Islam, a prayer type performed five times daily as a means of direct communication with Allah [6]. Meditating in Christianity consists of thinking about the characters and actions of their god in their lives and the Bible [7].

Hippocampal Atrophy in “Born-Again” Christians

A study cited by Clark et al. analyzed hippocampal atrophy in individuals affiliated with a religious conversion experience, more specifically “born-again” Christians. Hippocampal atrophy is an effect of aging, but can be combated with meditation, restoring some volume. New findings reveal individuals who have had a “life-changing

religious experience” had great increases in hippocampal atrophy in the right and left hemispheres via impaired memory, commonly seen in Alzheimer’s Disease patients. An unknown yet potential cause could be the stress of being a “religious minority [3]”.

Glossolalia in Christians

Glossolalia, also known as “speaking in tongues”, is presented in individuals whereby they experience different cerebral blood flow (CBF) than in regular speech. Those who experience this lose self-control by involuntarily speaking in a learned language. These abilities are connected to the frontal lobe. In 2018, Alexis E. Clark from the University of Arizona made mention of a study held with 5 Christian women with over 5 years of glossolalic practice engaged in singing and glossolalia. Both states were observed with a SPECT (single-photon emission computed tomography) scanner to measure regional cerebral blood flow (rCBF) afterwards. A SPECT scanner is a nuclear imaging testing type involving the use of radiotracers (radioactive substances) to capture 3D images of organs and tissues. This can show how well one’s organs function, brain region activity levels, & how well blood flows to the heart through the arteries and veins [9]. The most common are brain scans. Results had shown upon comparison of the two scans significant decreases in rCBF in the prefrontal cortex (in frontal lobe except for motor & premotor cortices; social behavior mod regulates attention, memory processing, & eration), left caudate (near center of brain, adjacent to thalamus; helps process visual information &

movement control), & left temporal lobe (behind ears; responsible for auditory processing & memory encoding). However, rCBF in the left (track body parts as they move) & right (responsible for spatial awareness) superior parietal lobe increased in those who involuntarily spoke in tongues but didn't consciously speak it, as they were in a singing state. Self-controlled and learned language abilities are derived from the frontal lobe and receive increased blood flow in terms of normal speech [3]. The practice of speaking in tongues shows how drastic the brain can cha

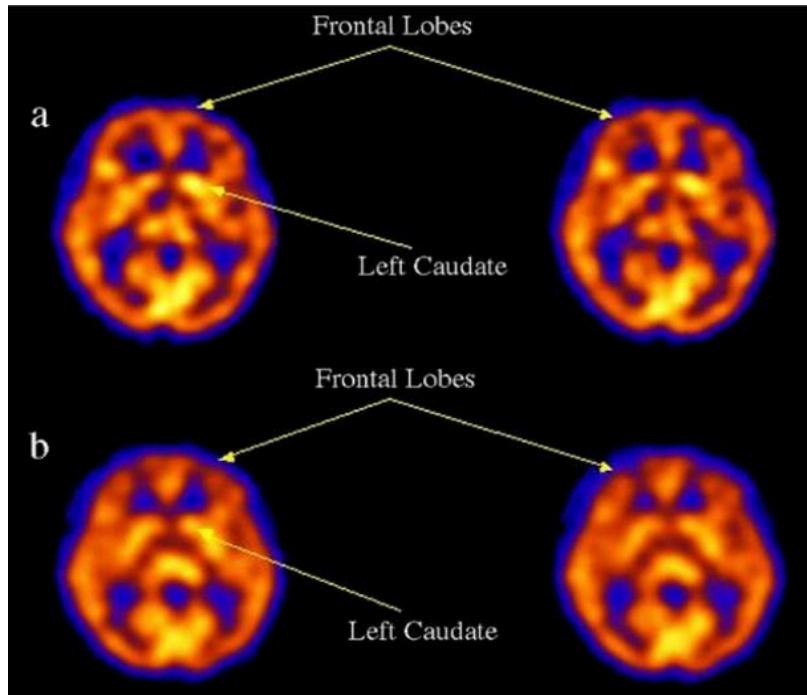


Figure 1. SPECT scans of participants in singing (a) and glossolalic (b) states. There are decreased rCBF levels in the right prefrontal cortex and left caudate via blood flow coloration. Red represents greater blood flow and blue less [3].

Intense Prayer in Dedicated Muslims

A follow-up study was held with three Muslim participants experienced in over fifteen years of intensive bouts of daily prayer (Dhikr, a form of Islamic worship in which one prays repetitively

in order to remember Allah, the Islamic god, and Salat, the second of the 5 pillars of Islam, a prayer type performed five daily as a means of direct communication with Allah) to see how CBF changed before and during prayer. A SPECT scanner was used to measure CBF afterwards. The results reaped a decrease in CBF and overall frontal lobe activity during intense prayer and increased activity of anterior cingulate gyrus of the third individual engaging in intense salat. The anterior cingulate gyrus (ACCg) is located within the front part of the cingulate cortex in the limbic system, ventral to the superior frontal gyrus. It is responsible for emotion & attention regulation, inhibitory control, error monitoring, & motivation [8]. This concludes that influenced brain structures are due to a high degree of spirituality and religiosity.

Sunday Assembly vs. Church-goers

Pew Research Center calculated ~28% of U.S. adults as “religiously unaffiliated” [10], also known as “nones” [7]. Nones are atheists (17%), agnostics (20%), or nothing in particular (63%) [8]. A study was conducted by Charles et al over secular Sunday-Assembly gatherings, deciphering if “secular rituals impact social bonding and emotional well-being” [11]. Ninety-nine adult (>18 years) participants (49 from Sunday Assemblies and 50 from churches) were recruited from four Sunday Assemblies in the UK (Central London, Reading, Bristol, and East End London) and four matched churches. Social bonding was measured on a 6-question scale. Five of the six were additionally measured on a 7-point Likert scale, including questions asked to the participants about connection, trust, & shared identity. The Positive and Negative Affect Scale (PANAS) was used to measure 20 emotions (10 positive, 10 negative) emotions on a 6-point Likert scale. Other measures include Sunday Assembly participants being asked to rate their religiosity and spirituality, and their connection to a higher power. Church-goers were asked to rate how religious they considered themselves. In the procedure, participants completed a pre-ritual questionnaire assessing their social bonding, affects, and religiosity/spirituality. The same measures were used to assess them in the

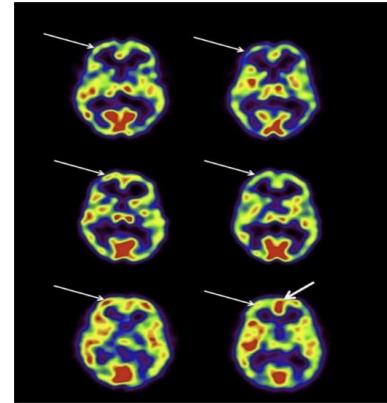


Figure 2. The SPECT scan shows participants in their control state (left column) compared to one in intensive prayer (right column). The arrows point to a decrease in frontal lobe activity in all three participants, and an increase of the anterior cingulate gyrus activity in only the third individual under intense salat [3].

post-ritual questionnaire. Researchers found that participation in them enhances feelings of connection and belonging among attendees while also improving mood, concluding shared secular rituals play a significant role in fostering social cohesion, similar to religious practices, but without the need for spiritual elements. There comes the outlier: is it about community or religion? A religious practice of fellowship and communing with fellow believers juxtaposes atheism, a lack of belief in the existence of one or more gods. A church in its essence is an institution of religious worship and fellowship with like-minded congregants. Replicating church culture by replacing Christian practices with atheist ones detracts from the core purpose of the gathering itself: the worship of one or more gods. Without innate reason to gather, excluding fellowship with people of the local community and discussing civic matters, making the results for the Assembly-Church study void, in the case of the Sunday Assembly attendees.

Conclusion

The limitations and/or biases in studies noted are the incorporations (or lack) of a religious upbringing, the mentioning of only Abrahamic, monogamous religions, excluding polytheistic and concept-based religions, like Buddhism and Confucianism. Afrin's review begins with an acknowledgment to the Christian god, saying, "I would like to thank the Almighty... [i]". The "Almighty" in this regard is a reference to the Christian God, potentially making the findings biased. Another limitation is the cultural differences in Abrahamic religions that differentiates the experiences of those who practice them. Brain activity could potentially differ based on region (U.S., Canada, etc.).

References

- [1] Afrin, Hosne Ara. (2021). THE IMPACT OF SOCIAL ISOLATION (SI) AND SOCIAL ENRICHMENT (SE) ON RAT HIPPOCAMPAL INTERNEURONS: A LITERATURE REVIEW (Doctoral dissertation, California State Polytechnic University, Pomona).
<https://scholarworks.calstate.edu/downloads/2f75rf4ot>. Retrieved: 24/10/2024
- [2] Rubin, R. D., et al. (29/09/2014). The role of the hippocampus in flexible cognition and social behavior. *Frontiers in Human Neuroscience*, 8(742). <https://doi.org/10.3389/fnhum.2014.00742>. Retrieved: 06/12/2024
- [3] Clark, A., et al. (2018). A LITERATURE REVIEW OF NEUROTHEOLOGY: HOW RELIGION AFFECTS THE BRAIN Item Type text; Electronic Thesis.
https://repository.arizona.edu/bitstream/handle/10150/630381/azu_etd_hr_2018_0028_sip1.m.pdf?sequence=1&isAllowed=y. Retrieved:
- [7] Pasley, M., & Forrest, T. (04/08/2022). Theology Thursday: A Christian Perspective on Meditation. GCU.
<https://www.gcu.edu/blog/theology-ministry/theology-thursday-christian-perspective-meditation>. Retrieved: 16/12/2024.
- [8] Gasquoine, P. G. (2013). Localization of function in anterior cingulate cortex: From psychosurgery to functional neuroimaging. *Neuroscience & Biobehavioral Reviews*, 37(3), 340–348. <https://doi.org/10.1016/j.neubiorev.2013.01.002>. Retrieved: 15/12/2024.
- [9] Cleveland Clinic. (21/09/2023). SPECT Scan: What It Does & Why You Might Need One. Cleveland Clinic.
<https://my.clevelandclinic.org/health/diagnostics/spect-scan>. Retrieved 18/11/2024.

- [4] Halliday, G. (2017). Pathology and hippocampal atrophy in Alzheimer's disease. *The Lancet Neurology*, 16(11), 862–864. [https://doi.org/10.1016/S1474-4422\(17\)30343-5](https://doi.org/10.1016/S1474-4422(17)30343-5). Retrieved: 13/12/2024
- [5] Mercadante, A., & Tadi, P. (24/07/2023). Neuroanatomy, Gray Matter. PubMed; StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK553239/>. Retrieved: 15/12/2024
- [6] Doufesh, H., Ibrahim, F., Ismail, N. A., & Wan Ahmad, W. A. (08/07/2014). Effect of Muslim Prayer (Salat) on α Electroencephalography and Its Relationship with Autonomic Nervous System Activity. *The Journal of Alternative and Complementary Medicine*, 20(7), 558–562. <https://doi.org/10.1089/acm.2013.0426>. Retrieved: 13/12/2024.
- [10] Nadeem, R. (24/01/2024). Religious “Nones” in America: Who They Are and What They Believe. Pew Research Center. <https://www.pewresearch.org/religion/2024/01/24/religious-nones-in-america-who-they-are-and-what-they-believe/#qr-who-are-the-nones-how-are-they-defined>. Retrieved: 29/10/2024.
- [11] Charles, S. J., et al. (2021). United on Sunday: The effects of secular rituals on social bonding and affect. *PLOS ONE*, 16(1), e0242546. <https://doi.org/10.1371/journal.pone.0242546>. Retrieved: 28/10/2024.

Nitrous oxide, Not Ketamine: An Alternative to Psychedelic Therapy

Ashley Keith

Introduction

Nitrous oxide, colloquially known as “laughing gas”, is the most common anesthetic utilized in surgery and dentistry. One of the most familiar uses for nitrous oxide outside of dentistry is its use as a frothing gas for whipped cream, which is also the main way the drug is sold and abused as a recreational drug. Research into recreational drugs as treatment options for mental illness has recently expanded in scope and legitimacy, with the FDA having approved nasally-administered ketamine [esketamine] for rapid-acting treatment for treatment-resistant depression in 2019. Recent research has also shown that nitrous oxide induces the same dissociative and hallucinogenic effects as ketamine but is distinctly less potent. This research, combined with the differences between the two drugs, both on a chemical and a circumstantial level, shows the efficacy of nitrous oxide as a safer and more appealing alternative to ketamine for rapid-acting antidepressant treatment.

Depression and Psychedelic Therapy

Establishing the context of the theorized use is important to understand how exactly nitrous oxide could be used as an antidepressant. Depression, specifically Major Depressive Disorder (MDD) is the main focus of ketamine treatment and is the disorder most studied in nitrous oxide treatment trials. MDD is a serious mood disorder that causes severe symptoms: behavioral abnormality, emotional instability, cerebral dysfunction, and even a vast array of serious physical side effects [1]. The current state of MDD treatment is highly problematic. All commercially available antidepressants only treat the neurotransmitter imbalances caused by depression, increasing levels of serotonin, norepinephrine, and/or dopamine, which does not treat the root issue of MDD: cognitive function on both neuronal and systematic levels [2] [3]. These medications also have severe side effects and safety concerns and do not even work for up to 50% of all depressed people [4]. This lack of consistent efficacy has been one of the main justifications for research into recreational drugs as alternative, and possibly far more effective, treatment options for MDD. Rather than attempting to fix the side effects of MDD, psychedelic therapy has shown the ability to transform the mind itself [5]. The reason why psychedelic treatment, which could be seen as a sort of miracle cure, has been obstructed as a treatment option for decades is due to a long history of

government intervention, negative socio-cultural perceptions, and lack of proper research and funding [5]. The timelines of nitrous oxide and ketamine are important to establish the context of how exactly such treatment has evolved.

History

Nitrous oxide was first synthesized in 1772 in England and used as an anesthetic by a dentist in 1844. It has been used recreationally for 200 years, dating back to “Laughing Gas parties” held for the British upper class at the turn of the 19th century [6]. This recreational abuse has stood the test of time, and nitrous oxide recently went viral on social media under the name “Galaxy Gas” [7]. At the same time, interest in using nitrous oxide for depression has reawakened. Nitrous oxide was explored for use in the treatment of psychiatric disorders and substance withdrawal and had already been proven to alleviate acute alcohol withdrawal between the 1980s and 2000s, but focus on the drug had been abandoned for almost fifteen years before research resumed [6].

Ketamine has a similar story. Synthesized in 1962 as a safer anesthetic alternative to phencyclidine (PCP) and first administered for human anesthetic use in 1964, ketamine was used extensively in the Vietnam War as a battlefield anesthetic [8] [9] [10]. The first recreational use of ketamine was recorded around the same time but did not become a popular drug until the 1990s European dance music scene. Since then, reports of recreational use have continued to rise [11].

Ketamine for Treatment-Resistant Depression

Ketamine’s efficacy as an antidepressant was discovered in 2000 and has been noted as one of the most important advancements in the treatment of depression in more than 50 years. Ketamine’s results became the basis for pursuing N-methyl-D-aspartate (NMD) antagonists for depression and permanently shifted the focus of antidepressant research and development toward psychedelic therapy [12]. Ketamine clinics tailored to treating mental illnesses began popping up in the early 2010s. They quickly grew into a multi-billion dollar industry and ketamine was approved by the FDA for antidepressant use in 2019 [13] [14]. While ketamine’s usefulness has already been solidly proven, not much evidence has been shown for nitrous oxide but multiple trials investigating the antidepressant efficacy of nitrous oxide have been approved or are currently underway, and many are likely to follow in the future [15]. Decades of trials and research led to the psychiatric use of ketamine as an antidepressant, and understanding the mechanisms behind these NMDA antagonist drugs is vital to justify nitrous oxide as an alternative to ketamine.

Mechanism of Action

The exact mechanism of nitrous oxide is unclear. Nitrous oxide’s psychoactive effects come from interactions with the nervous system, specifically how it affects certain neurotransmitter receptors. Neurotransmitters are chemical messenger molecules that allow neurons to communicate with each other by binding to and activating their respective receptors. Nitrous oxide acts predominantly as a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist [16].

NMDARs are receptors that allow Calcium into the neuron and are theorized to be a central part of the process of long-term potentiation (LTP, the strengthening and reinforcement of signaling between neurons). [17] NMDARs are thought to play a key role in the neurophysiology of depression, modulating the development and growth of neural connections. They're highly concentrated in brain areas important for higher-level thought, cognition, and emotion, like the hippocampus, amygdala, and prefrontal cortex. NMDAR overexcitation (frequent and excessive activation of the function) leads to an influx of excess calcium into the neuron, causing excitotoxicity (cell damage caused by overexcitation) and apoptosis. NMDAR antagonists reduce this excitatory signaling, especially in neural circuits related to stress and anxiety, which promotes new neural connections and the growth of healthy neurons [19].

NMDAR Antagonists and Psychoactive Effects

NMDAR antagonists are referred to as dissociative anesthetic drugs. Some commonly known dissociative drugs are ketamine, PCP, DXM, and nitrous oxide [20]. NMDAR antagonists block the function of NMDARs in inhibitory processes, allowing neurons to fire and connect freely. This kind of neural dysfunction is disorganized firing, as the synchronicity of neural firing is disrupted and alters the ability to process information in the brain [21]. The prevalence of NMDARs, especially in brain areas important to sensory processing, integration, and conscious operations, is what allows NMDAR antagonists to have their acute and uniquely dissociative psychoactive effects.

Have you ever felt an indescribably strange sensation after drinking cough syrup? That's dextromethorphan (DXM), an active ingredient in almost all over-the-counter cold medications. DXM is an NMDAR antagonist, which leads to the mildly dissociated feeling of confusion you may experience when taking cold medicine.

While the exact effects of NMDAR antagonists are heavily varied between different people, they are generally marked by their ability to cause dissociation and hallucinations, due to the previously mentioned NMDAR concentration among brain areas like the prefrontal cortex, amygdala, thalamus, and hippocampus. [22]. These effects may give a person a sense of "floating", euphoria, or an out-of-body experience. The acute potency of these effects differs heavily between different dissociatives, and like how ketamine was made as a less psychoactive anesthetic alternative to PCP, nitrous oxide could potentially act as a less psychoactive therapeutic alternative to ketamine.

Contrasts in Potency

Despite both drugs being NMDAR antagonists, nitrous oxide is magnitudes less psychoactive than ketamine. Nitrous oxide does not block NMDARs for as long, nor is it as strong as ketamine. Nitrous oxide has a half-life of five minutes while ketamine has a half-life of 2 to 4 hours [23]. This is because ketamine is metabolized in the liver and its metabolites prolong the psychoactive effects hours after administration.[24]. Nitrous oxide is not metabolized, as it is inhaled and exhaled, unchanged, through the lungs. [25].

This means that while ketamine must take effect and move through the body before its effects stop, nitrous oxide's effects cease immediately after it is no longer being inhaled. This is one of the important main differences between the two drugs, which could highlight its efficacy as an alternative to ketamine.

Ketamine is far more potent. In rare cases, even in clinical settings, ketamine can induce psychosis for up to 24 hours in healthy patients, exacerbate psychotic symptoms, and theoretically trigger new episodes in people with schizophrenia [26] [27]. Comparatively, the effects of nitrous oxide are so transient that the moment a patient reports any sort of possible issue, the treatment can cease immediately and no such psychotic side effects could develop.

Incorporated Elements of Psychotherapy

This leads to an important element of all drug-assisted psychotherapy. A feeling of control is critical to the self-perceived safety of a patient, which is something ketamine does not offer, but nitrous oxide does. A lack of control is a serious stress factor and possible emotional disruption for psychotherapy, it can make anxiety worse and distract a patient from the entire point and goal of their treatment. Another aspect of nitrous oxide that makes it possibly less anxiety-inducing than ketamine is its general appeal for treatment.

Familiarity

Nitrous oxide is nigh-universal in the world of dentistry. There is no fear of uncertainty when using nitrous oxide as almost everyone has been under the effects of "laughing gas" before. A sense of familiarity and comfort makes psychotherapy easier and makes using nitrous oxide for therapeutic purposes much more appealing to people who may not be willing to pursue ketamine therapy for a multitude of reasons.

Public Perception

One of these reasons is public perception and pre-existing assumptions about ketamine. The Gateway Foundation, self-described as "the country's largest nonprofit treatment provider specializing in substance abuse disorder treatment", classifies ketamine as a hard drug on its website [28]. The Gateway Foundation emphasizes that the public perception of "hard drugs" is based on misconception, but the fact ketamine is often lumped into the same category as heroin and crystal meth proves that major sections of the population may be unwelcoming to ketamine therapy. In 1999, ketamine became a Schedule III controlled substance alongside anabolic steroids and Vicodin [29].

Administration Circumstances

Combined with this with the fact ketamine is administered intravenously. Imagine having a needle put in your arm and being injected with a substance that you aren't familiar with and have only heard dangerous things about. The optics of such a scenario are likely unfavorable to many people. Nitrous oxide would be a generally more comfortable experience, as it is done through a gas

mask, and would be more appealing to a significant number of people who need psychedelic therapy but are hesitant due to the aforementioned circumstances. Some differences occur within the administration itself that could potentially make people adverse to ketamine. While both drugs can make someone nauseous, dizzy, cause anxiety, panic, or induce vomiting, these effects are far more common with ketamine [31]. Nitrous oxide's other common side effect in a clinical setting is headaches. Ketamine however can induce hypertension, and in rare cases, cystitis, a type of urinary tract infection [31].

Each of these substances has additional side effects not included in this section because they are extremely unlikely and virtually impossible to occur in a properly maintained clinical setting. A study from Science Translational Medicine shows that nitrous oxide can be administered at a 25% concentration with a similar efficacy to a 50% concentration with significantly fewer adverse side effects, something that cannot be done with ketamine [32].

Efficacy Research

The results of studies on each drug's efficacy for treatment-resistant depression treatment are positive and encouraging. Ketamine has dozens, possibly even hundreds of clinical trials for its antidepressant use, while nitrous oxide only has a handful but more trials are currently underway or have been approved. According to the Bio-K study, 52% of patients had remission from severe depression (a cessation of a majority of depressive symptoms) from ketamine alone [33]. A 2021 trial on nitrous oxide for depression treatment from Brazil shows that 90% of patients experienced a therapeutic response and 15% of patients experienced remission [34]. This data, however, comes from bio-marker studies and may not be a reflection of the post-treatment reality of the patients -- a serious point that needs discussion in the wider medical community.

In Practice: Ketamine Therapy's Pitfalls

In practice, ketamine therapy is dubious. Since intravenous ketamine is not approved by the FDA for depression, individual practitioners develop their own treatment protocols. These treatments are extremely expensive because they are not covered by insurance. Single sessions can cost between 300 and 800 dollars. Treatment is unregulated, inconsistent, and far too costly. In contrast, there are not as many administration variables for nitrous oxide and it is not nearly as expensive [35]. Ketamine injections alone may not even work for some people. In those cases, ketamine-assisted psychotherapy [KAP] is effective [36]. However, KAP is even more expensive and harder to obtain than simple ketamine injection therapy. A lack of consistent treatment protocols makes this issue even worse. KAP could be far more effective for some people, but the lack of proper availability wastes the potential benefits of treatment. On the other hand, nitrous oxide is extremely portable and cheap. These factors may open the way for nitrous oxide-assisted psychotherapy to be done as an alternative to KAP -- there is no current research to support this, though.

Abuse Potential

Nitrous oxide does not fit the criteria for dependency as it does not present physical withdrawal symptoms, but studies have shown the ability to induce mild psychological dependency [37]. Also known as whippets, nitrous oxide has a two-century-long history of recreational use. In the '60s, nitrous oxide was extremely popular in "hippie" scenes, and current usage reported among young adults has risen since 2000 [8] [38]. Nitrous oxide abuse has recently gone viral on social media following the reveal of Kanye West's chronic heavy abuse of nitrous oxide and a video showing a young man inhaling nitrous oxide from a massive tank labeled "Galaxy Gas" [39] [7]. Kanye West's abuse is so heavy that it's been theorized his abuse of the drug is why his music has declined in quality.

Side Effects of Abuse Potential

Nitrous oxide abuse's most common and severe side effect is its ability to permanently deactivate vitamin B₁₂. This deactivation leads to nitrous oxide-induced demyelination (NOID) which causes a wide array of effects including cell death, encephalopathy (brain dysfunction), and spinal cord degeneration. Spinal cord degeneration in particular is the main cause of NOID's peripheral neuropathy (inability to feel sensation in the limbs) and in some cases has even resulted in permanent paralysis [40]. Nitrous oxide abuse can also cause death due to hypoxia, a lack of oxygen, as the drug is often abused without the proper safety techniques to incorporate enough oxygen into the inhalation process [41] [42]. NOID's effects are proven to be reversible with early B₁₂ supplementation treatment [43].

Global Warming Contributor

Nitrous oxide is one of the most common environmental pollutants, both in and outdoors. It's a greenhouse gas, absorbing radiation and trapping heat in the atmosphere. It is considered a "super pollutant" since 1 kg of N₂O has the same impact on global warming as 273 kg of CO₂. It is the third most damaging greenhouse gas, responsible for roughly 6% of all climate warming. Industrial agriculture is responsible for 80% of nitrous oxide emissions, with 80% of that being due to the use of synthetic fertilizers. While nitrous oxide use in the medical industry is responsible for virtually none of its emissions, roughly 0.1 - 0.01%, medical offices need to maintain sustainable storage practices and minimize the waste of disposable equipment used in administration [44] [45].

Lack of Comparative and Psychiatric Research: Conclusion

Nitrous oxide and ketamine have close to no psychiatric studies that compare the efficacy of each drug within the same clinical settings. Nitrous oxide's mechanisms of action, while likely similar to those of ketamine, are largely unknown within themselves -- and ketamine's mechanisms, while far more researched, are still somewhat obscured. Most research into the efficacy of hallucinogenics as a form of treatment is in its early stages and extremely novel. On top of this, we are nowhere close to understanding the exact mechanisms behind mental illness. This leaves a lot to be desired for nitrous oxide -- until more research proves its efficacy, it will likely remain as nothing more than a mild anesthetic abused by young adults as a recreational drug.

References

- [1] Mayo Clinic. (14/10/2022). Depression (Major Depressive Disorder). Mayo Clinic; Mayo Foundation for Medical Education and Research. <https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007>. Retrieved: 19/12/2024
- [2] Penn, Elizabeth et al. (2/10/2012). The drugs don't work? antidepressants and the current and future pharmacological management of depression. Therapeutic Advances in Psychopharmacology, 2(5), 179–188. <https://doi.org/10.1177/2045125312445469>. Retrieved: 19/12/2024
- [3] Lam, Raymond et al. (2014). Cognitive Dysfunction in Major Depressive Disorder: Effects on Psychosocial Functioning and Implications for Treatment. The Canadian Journal of Psychiatry, 59(12), 649–654. <https://doi.org/10.1177/070674371405901206>. Retrieved: 19/12/2024
- [4] European College of Neuropsychopharmacology. (n.d.) Why don't antidepressants work in some patients? Mouse study shows it may be down to your environment. Media Release: European College of Neuropsychopharmacology. [Www.ecnp.eu](https://www.ecnp.eu/informationandnews/ecnp-press-office/Poggini). <https://www.ecnp.eu/informationandnews/ecnp-press-office/Poggini>
- Retrieved: 19/12/2024
- [5] Dobkin, Richard et al. (2019). The Past and Future of Psychedelic Science: An Introduction to This Issue. Journal of Psychoactive Drugs, 51(2), 93–97. <https://doi.org/10.1080/02791072.2019.1606472>
- Retrieved: 19/12/2024
- [6] Gillman, Mark. (11/6/2019). Mini-Review: A Brief History of Nitrous Oxide (N₂O) Use in Neuropsychiatry. Current Drug Research Reviews, 11(1), 12–20. <https://doi.org/10.2174/1874473711666181008163107>
- Retrieved: 19/12/2024
- [24] Dinis-Oliveira, Ricardo. (2017). Metabolism and metabolomics of ketamine: a toxicological approach. Forensic Sciences Research, 2(1), 2–10. <https://doi.org/10.1080/20961790.2017.1285210>
- Retrieved: 19/12/2024
- [25] No Author. (n.d.). Nitrous Oxide: Pharmacology, Signs/Symptoms, Patient Selection. https://bestdentalce.com/yahoo.site.admin/assets/docs/1.February_13.2021.Nitrous.Oxide.Pharmacology.Handout.4371633.pdf
- Retrieved: 19/12/2024
- [26] Beck, Katherine et al. (2020). Association of Ketamine With Psychiatric Symptoms and Implications for Its Therapeutic Use and for Understanding Schizophrenia. JAMA Network Open, 3(5), e204693. <https://doi.org/10.1001/jamanetworkopen.2020.4693>
- Retrieved: 19/12/2024
- [27] Yurgelun-Todd, Deborah et al. Yurgelun-Todd, D. A., Renshaw, P. F., Goldsmith, P., Uz, T., & Macek, T. A. (2019). A randomized, placebo-controlled, phase 1 study to evaluate the effects of TAK-063 on ketamine-induced changes in fMRI BOLD signal in healthy subjects. Psychopharmacology, 237(2), 317–328. <https://doi.org/10.1007/s00213-019-05366-1>
- Retrieved: 19/12/2024
- [28] Gateway Foundation. (12/7/2021). The Differences Between Hard and Soft Drugs | Gateway Foundation. Gateway Foundation. <https://www.gatewayfoundation.org/blog/hard-vs-soft-drugs/>
- Retrieved: 19/12/2024
- [29] Drug Enforcement Administration. (2020). Ketamine. <https://www.dea.gov/sites/default/files/2020-06/Ketamine-2020.pdf>
- Retrieved: 19/12/2024

- [7] Know Your Meme Contributors. (7/26/2024). My Name Lil T Man. Know Your Meme. <https://knowyourmeme.com/memes/my-name-lil-t-man>
- Retrieved: 19/12/2024
- [8] Li, Linda et al. (2016). Ketamine: 50 Years of Modulating the Mind. *Frontiers in Human Neuroscience*, 10(612). <https://doi.org/10.3389/fnhum.2016.00612>
- Retrieved: 19/12/2024
- [9] Peltonieme, Marko et al. Peltonieme, M. A., Hagelberg, N. M., Olkkola, K. T., & Saari, T. I. (3/30/2016). Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. *Clinical Pharmacokinetics*, 55(9), 1059–1077. <https://doi.org/10.1007/s40262-016-0383-6>
- Retrieved: 19/12/2024
- [10] Domino, Edward. (2010). Taming the Ketamine Tiger. *Anesthesiology*, 113(3), 1. <https://doi.org/10.1097/ALN.0b013e3181ed09a2>
- Retrieved: 19/12/2024
- [11] Stewart, Ashleigh et al. (8/4/2021). Ketamine Use Among People Who Regularly Use Ecstasy and Other Illicit Stimulants in Australia: Trends and Characteristics of Use, 2009–2019. *Journal of Studies on Alcohol and Drugs*, 82(2), 188–196. <https://doi.org/10.15288/jasad.2021.82.188>
- Retrieved: 19/12/2024
- [12] Singh, I et al. (2017). Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight - UCL Discovery. <https://discovery.ucl.ac.uk/id/eprint/1552865/>
- Retrieved: 19/12/2024
- [13] Peskin, Evan et al. (28/1/2023). Increased demand for ketamine infusions and associated complexities. *Journal of Pain Research*, Volume 16, 295–299. <https://doi.org/10.2147/jpr.s403323>
- Retrieved: 19/12/2024
- [30] Hantson, Ph. et al. (1996). Toxic gases. *Human Toxicology*, 661–669. <https://doi.org/10.1016/b978-044481557-6/50028-9>
- Retrieved: 19/12/2024
- [31] Chang, Minna et al. (2024). Ketamine cystitis following ketamine therapy for treatment-resistant depression – case report. *BMC Psychiatry*, 24(1). <https://doi.org/10.1186/s12888-023-05468-3>
- Retrieved: 19/12/2024
- [32] Nagele, Peter et al. (2021). A phase 2 trial of inhaled nitrous oxide for treatment-resistant major depression. *Science Translational Medicine*, 13(597), eabe1376. <https://doi.org/10.1126/scitranslmed.abe1376>
- Retrieved: 19/12/2024
- [33] Vande Voort, Jennifer et al. (15/3/2022) The BIO-K Study: A Single-Arm, Open-Label, Biomarker Development Clinical Trial of Ketamine for Non-Psychotic Unipolar Major Depression and Bipolar I or II Depression. (Bio-K). *ClinicalTrials.gov*, Mayo Clinic. <https://clinicaltrials.gov/study/NCT03156504>
- Retrieved: 19/12/2024
- [34] Guimaraes, Mara. (2021). Nitrous oxide as an adjunctive therapy in major depressive disorder: a randomized controlled double-blind pilot trial. *Brazilian Journal of Psychiatry*, 43(5), 484–493. <https://doi.org/10.1590/1516-4446-2020-1543>
- Retrieved: 19/12/2024
- [35] Megli, D (30/1/2024) The ketamine economy: New mental health clinics are a “Wild West” with few rules. *NPR*. <https://www.npr.org/sections/health-shots/2024/01/30/1227630630/ketamine-infusion-clinic-mental-health-depression-anxiety-fda-off-label>
- Retrieved: 19/12/2024
- [36] An Introduction to Ketamine-Assisted Psychotherapy (n.d.). Psychology Today. <https://www.psychologytoday.com/us/blog/new-beginning/202208/introduction-ketamine-assisted-psychotherapy>

-
- Retrieved: 19/12/2024
- [14] No Author. (n.d.) U.S. Ketamine Clinics Market Size & Share [2023 Report]. [Www.grandviewresearch.com](http://www.grandviewresearch.com).
<https://www.grandviewresearch.com/industry-analysis/us-ketamine-clinics-market-report>
- Retrieved: 19/12/2024
- [15] Myles, Payla et al. (24/6/2023). Treatments for major depression. *The Lancet*, Volume 401, 2111.
[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(23\)00950-0/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)00950-0/fulltext)
- Retrieved: 19/12/2024
- [16] Savage, Sinead et al. (2014). The Neurotoxicity of Nitrous Oxide: The Facts and “Putative” Mechanisms. *Brain Sciences*, 4(1), 73–90. <https://doi.org/10.3390/brainsci4010073>
- Retrieved: 19/12/2024
- [17] Hansen, Kasper et al. (2018). Structure, function, and allosteric modulation of NMDA receptors. *The Journal of General Physiology*, 150(8), 1081–1105. <https://doi.org/10.1085/jgp.201812032>
- Retrieved: 19/12/2024
- [18] Réus, Gislaine et al. (2016). Glutamatergic NMDA Receptor as Therapeutic Target for Depression. *Ion Channels as Therapeutic Targets, Part A*, 169–202.
<https://doi.org/10.1016/bs.apcsb.2015.10.003>
- Retrieved: 19/12/2024
- [19] Egunlusi, Ayodeji et al. (2024). NMDA Receptor Antagonists: Emerging Insights into Molecular Mechanisms and Clinical Applications in Neurological Disorders. *Pharmaceuticals*, 17(5), 639. <https://doi.org/10.3390/ph17050639>
- Retrieved: 19/12/2024
- [20] Zhang, Wenbo et al. (2022). Targeting NMDA receptors in neuropsychiatric disorders by drug screening on human neurons derived from pluripotent stem cells. *Translational Psychiatry*, 12,
- Retrieved: 19/12/2024
- [37] Back, Sudie et al. (2023). Does nitrous oxide addiction exist? An evaluation of the evidence for the presence and prevalence of substance use disorder symptoms in recreational nitrous oxide users. *Addiction*, 119(4). <https://doi.org/10.1111/add.16380>
- Retrieved: 19/12/2024
- [38] Hussain, Zainab. Nitrous oxide: Doctors warn of “epidemic” of use by young people. *BMJ*, o2155.
<https://doi.org/10.1136/bmj.o2155>
- Retrieved: 19/12/2024
- [39] RapTV Staff. (26/7/2024) Ye’s Alleged History With Nitrous Oxide Usage. RapTV.
<https://raptv.com/article/yes-alleged-history-with-nitrous-oxide-usage/>
- Retrieved: 19/12/2024
- [40] Noh, Thomas et al. (2020). Nitrous oxide-induced demyelination: Clinical presentation, diagnosis and treatment recommendations. *Journal of the Neurological Sciences*, 414, 116817. <https://doi.org/10.1016/j.jns.2020.116817>
- Retrieved: 19/12/2024
- [41] Brodsky, Jay et al. (1986). Adverse Effects of Nitrous Oxide. *Medical Toxicology*, 1(5), 362–374.
<https://doi.org/10.1007/bf03259849>
- Retrieved: 19/12/2024
- [42] Backman, Isabella (8/1/2024). Nitrous Oxide Effects Are Reversible With Early Treatment. *Medicine.yale.edu*.
<https://medicine.yale.edu/news-article/nitrous-oxide-effects-are-reversible-with-early-treatment/>
- Retrieved: 19/12/2024
- [43] EIA. Nitrous oxide - EIA. (2020). [Eia-International.org](https://eia-international.org/climate/nitrous-oxide/).
<https://eia-international.org/climate/nitrous-oxide/>

243. <https://doi.org/10.1038/s41398-022-02010-z>

Retrieved: 19/12/2024

Retrieved: 19/12/2024

[21] Molina, Leonardo et al. Molina, L. A., Skelin, I., & Gruber, A. J. (2014). Acute NMDA Receptor Antagonism Disrupts Synchronization of Action Potential Firing in Rat Prefrontal Cortex. PLoS ONE, 9(1), e85842. <https://doi.org/10.1371/journal.pone.0085842>

Retrieved: 19/12/2024

[44] McGain, Forbes et al. (2020). Environmental sustainability within anaesthesia and critical care. British Journal of Anaesthesia, 125(5). <https://doi.org/10.1016/j.bja.2020.06.055>

Retrieved: 19/12/2024

[22] Khesmaki, Malahat et al. (2023). The role of glutamate NMDA receptors of the mediodorsal thalamus in scopolamine-induced amnesia in rats. Neuroscience Letters, 820, 137595. <https://doi.org/10.1016/j.neulet.2023.137595>

Retrieved: 19/12/2024

[23] Alai, Ally. (2019). Nitrous Oxide Administration: Overview, Indications, Contraindications. EMedicine. <https://emedicine.medscape.com/article/1413427-overview>

Retrieved: 19/12/2024



DISEASES & DISORDERS

Virtual Reality and its Impact on Alzheimer's Disease

Samuel Mayers

Abstract

Virtual reality technology has shown to improve multiple aspects of memory as well as the emotional wellbeing of those suffering from Alzheimer's disease (AD). Starting with the former, episodic memory and prospective memory performance in participants with mild AD saw noticeable improvements when study participants were exposed to virtual environments that allowed them to actively navigate their environment without exhausting them emotionally and virtual tasks with emotionally-positive connotations or aspects. The emotional wellbeing of those suffering from AD was improved after exposing them to 360° videos portraying desired travel locations played through a headset or through self-selected virtual environments, some of which were similar to real-life environments visited by the participant which they had a strong emotional connection to. Taking into account the results of multiple studies, the inconsistencies of said studies, and the limitations of the studies conducted on this topic, more research on the use of such technologies is required to obtain a greater understanding of how to properly wield it and its intricacies.

Introduction

Alzheimer's disease is the most common form of dementia which affects 9.9 million people annually [1], remains as a disease without a cure and, some would argue, without adequate treatment. Virtual reality (VR) systems have recently seen implementation in certain aspects of healthcare, and have shown great promise as a treatment for Alzheimer's in test environments. Alzheimer's is a slow-progressing neurodegenerative disease that worsens over the course of multiple years. A person suffering from Alzheimer's will develop cognitive deficits that gradually worsen, with memory being affected by the disease first.

Memory can be divided into multiple domains with numerous subdomains yet. Take, for example, retrospective memory. This type of memory, which is the brain's ability to recall past information, can be further divided into multiple other categories, which includes episodic memory and prospective memory . Episodic memory encompasses long-term memories, including information such as location and time. Prospective memory, however, is the ability to remember to act on actions planned in the past. "Remembering to remember before one is to remember," to state it simply. This loss in cognitive function, especially memory, can lead one with Alzheimer's to slowly lose their independence by causing them to forget the most basic acts of daily living crucial for maintaining health and wellbeing. This may lead to a caretaker being introduced, likely making the current situation more stressful for the one suffering from Alzheimer's as well as their family.

On the topic of mood and behavior, Alzheimer's can also cause the sufferer to develop mood and behavioral disorders, making the situation more difficult for those involved. These disorders only have the potential to compound the level of emotional distress and pain that the sufferer is feeling. Though medication may solve the issue temporarily by alleviating symptoms, the issue may still remain. There may be an alternative to this method of treatment, however. Virtual reality (VR) technology has the potential to improve the emotional state and memory in those suffering from Alzheimer's.

To state it simply, VR technology is an umbrella for technologies that place a user in a 3-dimensional virtual environment that stimulates one or more of a user's senses. This technology can range from non-immersive (a user is not immersed in the virtual environment and can still interact with reality) to immersive (a user is fully immersed in the virtual environment and cannot adequately interact with the material world). These technologies can be coupled with other treatments, such as music therapy, in order to either create a tailored experience for someone with their unique situation or to amplify the effects of another treatment. It is because of the extent to which this technology can be personalized as well as its flexibility as far as environments and elements are concerned that make VR technology such a fantastic candidate for implementation in healthcare; in this case, Alzheimer's treatment. This flexibility allows for this technology to be tuned in a way that encourages the user to exercise their long- and short-term capabilities, which has been shown to improve their performance in these areas in a multitude of studies.

A gradual decline in short- and long-term memory capabilities is arguably one of the most widely known symptoms of Alzheimer's; greater attention is paid to technologies that can slow or even halt this decline because of this. When this question was presented when referencing VR

technologies, a multitude of studies on this topic responded with conflicting results. A study titled “Virtual Reality-Based Cognitive Stimulation on People with Mild to Moderate Dementia due to Alzheimer’s Disease: A Pilot Randomized Controlled Trial” argues that no improvement was observed after VR treatment, citing that results from trials such as the Clinical Dementia Rating, Clock Drawing Test, and the Trail Making Test prove this [2].

The Effect of VR Technology Use on Memory in AD Patients

To briefly describe these trials: the Clinical Dementia Rating evaluates an individual’s cognition, behavior, and ability to adequately perform activities of daily living, ranking the person’s aptitude on a scale of 0-3 once before testing and once after testing; the Clock Drawing Test evaluates a person’s executive, visuospatial (the ability to conjure, mentally manipulate, and analyze objects), and constructive functions using a paper-and-pencil-based instrument; the Trail Making Test assesses performance of multiple functions and is divided into two tests: part A and part B. Part A of the Trail Making Test assesses a person’s information processing capabilities, motor coordination, and attention span, while part B of the Trail Making Test assesses executive functions (i.e. working memory, sense of time, emotional regulation, among other functions) as well as mental flexibility. Part A does this by having test participants write down numbers in ascending order in a line drawing on an A4-size sheet of paper. Part B assesses these functions by having participants complete a similar activity as part A, albeit with letters being introduced. Participants are to place numbers and letters on a line in ascending order alternately, with numbers being organized in numerical order and letters being organized in alphabetical order. This study found that, of the tests performed, no statistically significant differences between the performance of the control and experimental groups were found. What little differences were discovered were negligible [2].

Based on the results of this one study, one would come to the conclusion that VR cannot be used as an effective treatment for Alzheimer’s disease. However, if one is to explore further and read more studies, literature reviews, study analyses, and the like, one will soon find the answer is not so simple. Take, for example, a study titled “Affective Out-World Experience via Virtual Reality for Older Adults Living with Mild Cognitive Impairments or Mild Dementia,” which experimented with VR as a treatment for those suffering from Alzheimer’s alongside those suffering from mild cognitive impairment (MCI) and other forms of dementia [3]. Though this study explores VR as a treatment for more than just Alzheimer’s, results from treatment of these other disorders through VR will not be referenced as heavily to maintain a focus on such

technology being used as a treatment for Alzheimer's.

This study, conducted by Maria Matsangidou among others in 2023, contains information that is able to be used to support the idea that the use of VR technology as a treatment for Alzheimer's can be effective. This study immersed thirty participants aged between 55 and 87 in virtual environments of their choosing (limited selection on a piece of A4-sized paper) for fifteen minutes (5 minutes allotted for 3 environments). An interview would then be conducted after the participant has finished experiencing their three chosen virtual environments. Though VR technology was not explicitly stated to have had an effect on memory, the emotions it invoked did. It was found that, during the participant's immersion in VR experiences, they would reminisce about previous real-life experiences. This shows that experiences of similar immersiveness to that shown in the study which possess elements similar to those from a memory of the participant's can aid in the recall of associated memories [3]. This stimulated resurfacing of memories has the potential to strengthen the process of memory recall. Before memory as a whole is discussed any further, some of its many facets which are pertinent to the discussion should be mentioned.

Memory is its own category entirely, and should be referenced as such. There exists multiple facets of memory, not only just the short- and long-term memories people associate with the word. Because of this expansiveness, only two forms of memory pertinent to this topic specifically will be discussed: prospective memory and episodic memory. This is because the two are, according to the elderly, the most prone to degradation. Visible issues with the two are also some of the earliest signs of dementia. Prospective memory, which is the ability to recall plans to execute actions formed in the past, will be elaborated on first.

VR technology has been shown to improve prospective memory and its aspects in a variety of studies; many of these were represented in a review titled "Being in the Past and Perform the Future in a Virtual World: VR Applications to Assess and Enhance Episodic and Prospective Memory in Normal and Pathological Aging." Using three studies, which are titled "Cognitive and neural plasticity in older adults' prospective memory following training with the virtual week computer game," "Virtual reality-based prospective memory training program for people with acquired brain injury," and "Event-based prospective memory in patients with Parkinson's disease: the effect of emotional valence" respectively, this review determined that VR does improve the prospective memory performance of users by presenting emotionally-enriched tasks to them. In a semi-immersive VR experience, participants were given a task with either positive (e.g. "tell Roberta that Maria had a baby when you talk to Roberta"), neutral (e.g. "Buy your bus ticket after

breakfast”), or negative (e.g. “Pay a fine for speeding when you go shopping”) emotional value. In participants not suffering from any neurodegenerative diseases as well as those suffering from neurodegenerative diseases such as Parkinson’s disease, it was found that performance when completing tasks with positive emotional value was better than performance when completing tasks with neutral or negative emotional value. It is of note that the performance of those suffering from neurodegenerative diseases was poorer than those not suffering from neurodegenerative diseases. The participants’ ability to recall the plan to complete tasks when task content is pleasant was also stronger than if the task was neutral, likely because positive stimuli causes participants to allocate more attention resources to the task. These studies also found few negative side effects after use of the program. All of this, coupled with how these experiences can be addictive and quite immersive, shows that immersive tasks such as these are capable of being used for the elderly either as treatments or for improving emotional state or condition [4]. Virtual experiences that focus on the completion of tasks with positive value have been shown to improve prospective memory performance in those with neurodegenerative diseases, sure; but this shouldn’t overshadow the effects VR technology has had on episodic memory, though.

VR technology has been shown to improve episodic memory performance as well. In the same review featuring evidence that VR technology improves prospective memory performance, episodic memory performance improvements due to VR use were also described. The review referenced an experiment conducted by Benjamin Rich Zendel among others, which introduced Super Mario 64 as a means to improve the mental aptitude of elderly users because of its 3D platform elements. The study found that users experienced an increase in grey matter concentration in regions that commonly see a decrease in thickness due to cognitive decline [5]. This increase could be further stimulated by immersing users in a virtual experience using VR technology, as it was suggested that greater immersion leads to greater increases in grey matter concentration in these commonly affected regions. When using this sort of technology as a treatment. These higher levels of presence in virtual experiences have been linked to improved factual memory performance and greater emotional stimulus impacts. Episodic memory performance can be further improved by having the user experience the virtual world from the perspective of their own body, as such results in more accurate episodic memory encoding. Active exploration of the virtual experience also improves performance, though certain types of this sort of exploration do have greater impacts than others. To support this, a study conducted by Najate Jebara as well as other researchers found that of four types of interaction when situated in a car in a virtual city, which include “passive” (users are passengers in a virtual car and cannot decide on the car’s route), “itinerary control” (users can choose the car’s route), “low control” (user is able to drive

the car, but can only move about the world a certain way because the car is driven on rails), and “high control” (users are the driver and can choose the direction in which the car is moving), types of interaction where the user’s control of the vehicle is low or when the user is responsible for choosing the route saw the best episodic memory scores out of the four. This means that prompting the use of multimodal coding (interaction through multiple stimulus pathways) with motor interaction through active navigation improves episodic memory performance so long as the interaction isn’t overly taxing in terms of attention [4]. Inconsistencies have been seen in results from experiments using VR to improve memory, however; meaning that portions of this information could be only partially true. Therefore, a sector of the human psyche that has seen consistent improvements through VR use must be referenced: emotional state.

The results when it comes to if VR technology can improve certain facets of memory or memory as a whole are inconclusive. Because of this, another aspect of the human mind is to be taken into consideration to determine whether or not VR is to be used to treat Alzheimer’s: emotions. VR experiences can be created and tailored to positively affect the quality of life of those suffering from Alzheimer’s.

The Effect of VR Technology Use on the Emotional State of AD Patients

It should come as no surprise that virtual experiences can improve the emotional state of the participant experiencing them. It has been shown that experiences involving or representing activities favorable to the participant or activities the participant experienced in the past can trigger activity in the brain’s reward system. This is a network of structures that connect the limbic system, includes the midbrain, and prefrontal cortex, includes the amygdala, ventral tegmental area, and nucleus accumbens. These structures serving various different functions work in conjunction with one another to produce feelings of pleasure or satisfaction in response to certain internal and external stimuli. This structure is perhaps best known for its main neurotransmitter: dopamine. To explain what exactly a neurotransmitter is, a neurotransmitter is any sort of chemical used to transmit information from one neuron to another. This neurotransmitter is both synthesized and released. Synthesis is largely conducted by the ventral tegmental area. Dopamine controls multiple facets of mood and emotional regulation as well as movement and coordination; though its role in motivation, inducing the sense of pleasure, reducing stress, and reward are best known. Dopamine reduces stress by suppressing the release of cortisol, a known stress-inducing hormone. This neurotransmitter influences a person’s behavior by instating or reinforcing pleasure-seeking and learning behaviors. It is dopamine that is released when participants are immersed in environments they deem pleasurable and is partly responsible for the results seen in

some of these studies [1]. To illustrate this, a study found that exposure to self-selected environments for 15 minutes total (5 minutes per environment) reduced participant anxiety [3]. It is the release of dopamine and suppression of the release of cortisol that caused this [1]. To give another example, in a study which used VR technology to display 360-degree videos of natural environments, travel destinations, and other favorable environments as a treatment for Alzheimer's found that participants who either had mild cognitive impairment or, more pertinent to this topic, mild dementia, experienced reduced feelings of apathy and depression than they had before they had been immersed in the virtual environment [6]. These examples illustrate how VR technology, or at least some forms of it, can improve the emotional state of Alzheimer's patients.

The use of this technology in this way does have its drawbacks, however. A study titled "Affective Out-World Experience via Virtual Reality for Older Adults Living with Mild Cognitive Impairments or Mild Dementia" found that participants who were immersed in an environment that connected to a past experience in some way experienced side effects such as disorientation or sadness when removed from the virtual experience and placed back into the real world [3]. When stripped of reward-inducing stimuli, the brain's reward system will begin to actively seek such stimuli again to continue producing dopamine. This exact process is responsible for addiction to substances, activities, or objects [1]. It is because of this that one must be careful when handling VR technology when such is used to treat patients.

Biases and Limitations

As one can see, conflicting information seems to appear on many fronts of this topic. This is because there exist a multitude of different factors that cause this immense variety in results. For one, VR technology does not refer to just one program or just one device; rather, it is an umbrella of different programs, devices, and systems that can differ greatly from one another. To compare two of the studies used, a trial titled "Virtual Reality-Based Cognitive Stimulation on People with Mild to Moderate Dementia due to Alzheimer's Disease: A Pilot Randomized Controlled Trial" used the Systemic Lisbon Battery, which is a non-immersive VR program that can be used to design and create virtual experiences that contain within them tasks mimicking typical activities of daily living. The specific program used in this medical trial contained 9 total tasks the participant had to complete. These tasks include: (T₁) Morning hygiene, (T₂) Shoe closet test, (T₃) Wardrobe test, (T₄) Memory test, (T₅) Virtual kitchen, (T₆) TV news, (T₇) Grocery store, (T₈) Pharmacy, and (T₉) Art gallery test (Oliveira, et al., 2021). Tasks 1-6 took place inside of a virtual apartment while tasks 7-9 involved the participant navigating a virtual city to reach a certain location to complete a

task. In a study titled “EEG Analysis of the Contribution of Music Therapy and Virtual Reality to the Improvement of Cognition in Alzheimer’s Disease,” on the other hand, participants were immersed in a virtual experience resembling a theater created using Unity 3D software. This virtual experience placed the participant in a seat in the center of the theater to allow for easy viewing of the stage, which was obscured by two red curtains when inactive. When active, the curtains on the theater’s stage would open, revealing the stage area and the animated instruments on said stage. The chosen songs, which include “Ave Maria” by Franz Schubert, “Eine Klein Nachtmusik: Allegro” by Mozart, “Ukulele” by Bensound, “Clair De Lune” by Debussy, “La Vie En Rose” by Edith Piaf, “Everyday” by Buddy Holly, “La Bamba” by Ritchie Valens, and “What A Wonderful World” by Louis Armstrong, would be played on these instruments. These songs were played in this order, with the curtains closing and opening once more to separate each song. To test the results of the treatment, the participant would then be immersed in another virtual experience resembling an apartment where they would complete several memory and attention exercises. In this trial, the attention exercises listed will be completed by the participant in the following order: an exercise where the participant has to list a set of numbers in the order they are spoken or in reverse order, an exercise where the participant presses the spacebar of a keyboard every time they hear the letter “A” in a series of letters spoken at one letter per second, and an exercise where the participant selects one of four letters that corresponds with the first letter of an object they are shown. The memory exercises will then be completed by the participant in the following order once they have completed the attention exercises: an exercise where the participant is visually or aurally presented an object and must determine whether or not they saw or heard it, an exercise where the participant must memorize the sequence a series of circles on a wall appear in, and an exercise where the participant memorizes a set of three pictures presented in a short period of time and chooses a set that matches the one they were first given [i].



Figure 1. A capture of the virtual stage seen in an experiment by Byrns, et. al. while one of the songs was being played [1].

Another glaring issue concerning the use of VR programs as treatments for Alzheimer's is the lack of research on these programs. As stated in studies titled "It Makes You Feel That You Are There": Exploring the Acceptability of Virtual Reality Nature Environments for People with Memory Loss," "Affective Out-World Experience via Virtual Reality for Older Adults Living with Mild Cognitive Impairments or Mild Dementia," and "Being in the Past and Perform the Future in a Virtual World: VR Applications to Assess and Enhance Episodic and Prospective Memory in Normal and Pathological Aging," the use of this technology as a treatment for Alzheimer's and other neurological disorders is still in its infancy. If more research were to be conducted, it is likely a definitive answer would be reached. One must also account for the regions these studies occurred in. Foreign regions are bound to have foreign cultures, which could lead to dramatically different reactions from participants when interacting with certain technologies. An example would be "Virtual Reality-Based Cognitive Stimulation on People with Mild to Moderate Dementia due to Alzheimer's Disease: A Pilot Randomized Controlled Trial," which was conducted in Portugal on Portuguese adults. While it is unlikely that this played as large a role in the variations in results between studies, it still likely played a role in differing results and is to be considered. Finally, one must also take into account the differences in sample size of these studies. A sample size of 14 as described in a study titled "Affective Out-World Experience via Virtual Reality for Older Adults Living with Mild Cognitive Impairments or Mild Dementia" is not representative of the entire population of those with Alzheimer's; thus, it should not possess as much weight as

a study with a sample size appropriate for the population being tested.

Conclusion

To state it simply, more research is needed to give a definitive answer on whether or not VR technology can be used to improve the memory and emotional state in those with Alzheimer's. This does not mean that the information presented is without value, though. Studies such as these provide information that can be used to form hypotheses and can be used as a starting point for future studies. Not only this, but it also offers a glimpse into the effects VR systems can have on those with Alzheimer's. Such glimpses are what fuel curiosity and encourage further research. Thus, such studies will accurately answer the questions they posed in time through others that studied them.

References

- [1] Byrns, Alexie et al. (24/8/2020). EEG Analysis of the Contribution of Music Therapy and Virtual Reality to the Improvement of Cognition in Alzheimer's Disease. Journal of Biomedical Science and Engineering. <https://www.scirp.org/journal/paperinformation?paperid=102398>. Retrieved: 11/10/2024.
- [2] Oliveira, Jorge et al. (16/5/2021). Virtual Reality-Based Cognitive Stimulation on People with Mild to Moderate Dementia due to Alzheimer's Disease: A Pilot Randomized Controlled Trial. International Journal of Environmental Research and Public Health. <https://www.mdpi.com/1660-4601/18/10/5290#B46-ijerph-18-05290>. Retrieved: 11/10/2024.
- [3] Matsangidou, Maria et al. (2023). Affective Out-World Experience via Virtual Reality for Older Adults Living with Mild Cognitive Impairments or Mild Dementia. International Journal of Environmental Research and Public Health. https://www.proquest.com/docview/2779561905/DrDA4FFCB6B6_4AEDPQ/r?accountid=210630&sourcetype=_Scholarly%20journals. Retrieved: 11/10/2024.
- [4] Rizzo, Azzurra et al. (2020). Being in the Past and Perform the Future in a Virtual World: VR Applications to Assess and Enhance Episodic and Prospective Memory in Normal and Pathological Aging. Frontiers in Aging Neuroscience. <https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2014.00338/full>. Retrieved: 11/10/2024.
- [5] West, Greg et al. (6/12/2017). Playing Super Mario 64 increases hippocampal grey matter in older adults. PLOS One. <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0187770>. Retrieved: 10/11/2024.
- [6] Brimelow, Rachel et al. (4/3/2020). Preliminary Research: Virtual Reality in Residential Aged Care to Reduce Apathy and Improve Mood. Marie Ann Liebert Incorporated publishers. Cyberpsychology, Behavior, and Social Networking Volume 23, Number 3. Retrieved: 16/12/24.

The Role of Astrocytes in Schizophrenia

Jesus Juan

Abstract

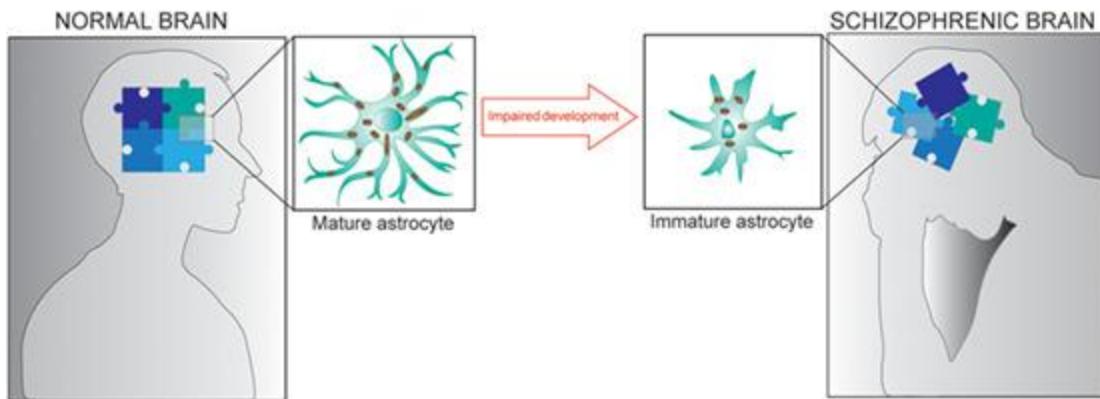
Schizophrenia is a complex neurodevelopmental disorder marked by cognitive, emotional, and behavioral impairments. Emerging evidence has highlighted the roles of mitochondrial dysfunction and astrocyte deficiencies in its pathogenesis. Mitochondrial abnormalities found in schizophrenia and 22q11 deletion syndrome disrupt energy metabolism, affecting astrocyte maturation and synaptic pruning. Astrocytes regulate synapse formation, brain homeostasis, and prefrontal cortex development, where structural and functional alterations contribute to cognitive dysfunction. Deficient astrocyte markers and impaired mitochondrial pathways suggest interconnected mechanisms driving SCZ symptoms. Understanding these interactions offers insight into brain disorders and may lead to novel therapeutic approaches for schizophrenia and related conditions.

Introduction

Schizophrenia is a permanent neurodevelopmental disorder that distorts the way someone thinks, behaves, perceives reality, expresses emotions, and relates to others. It affects approximately one percent of the global population and alters brain structure and function, which causes symptoms that are divided into three categories: positive symptoms (delusions, hallucinations, disorganized thinking (speech), extremely disorganized or abnormal motor (movement) behavior), negative symptoms (decreased motivation, anhedonia (reduced experience of pleasure), blunted affect (unable to express emotions), alogia (reduction of quality of words spoken), and asociality), and cognitive symptoms (impairments in working memory, difficulties with executive functions, and attention deficits). Schizophrenia isn't well understood in terms of its exact cause. Still, emerging evidence suggests that astrocytes may play a major role in its progression and could possibly explain some of its symptoms.

In early childhood, the brain has roughly twice the synapses, compared to an adult. During adolescence, the unnecessary synapses are removed. This is called synaptic pruning which is a process that involves microglia phagocytizing synapses. Microglia get rid of synapses by eating them, helping shape brain connections during development and keeping the brain healthy. While synaptic pruning takes place, astrocytes maintain and construct neural circuitry by releasing gliotransmitters (D-serine, glutamate, and ATP), which bind to receptors to cause synaptic transmission (neuron signaling). The regularity of the usage of certain synapses strengthens them while the unutilized

ones will be marked for elimination. This optimizes brain function and enhances neural efficiency [1] but individuals with SCZ are shown to have deficits in astrocytes. Therefore, astrocytes could be the missing piece to improving treatment outcomes or resolving the causation of Schizophrenia.

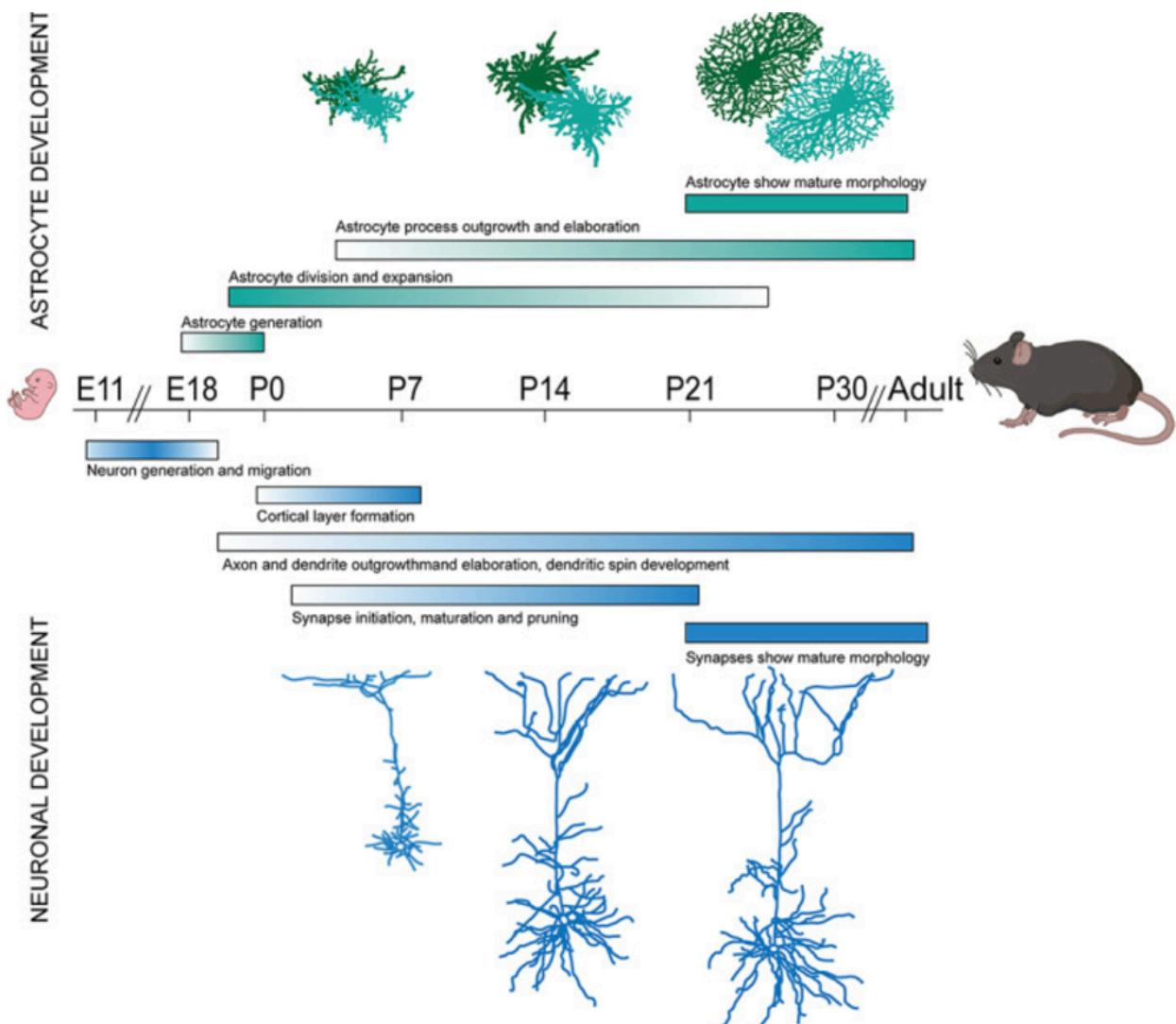


In schizophrenia, impaired astrocyte maturation affects brain function by disrupting synaptic pruning and energy support for neurons [16].

The Role of Mitochondrial Dysfunction in Schizophrenia

A prominent indicator of Schizophrenia is abnormal mitochondrial functioning that has been found using magnetic resonance spectroscopy and brain activity tests on SCZ patients [2]. Mitochondria are organelles whose role is to produce energy in the form of Adenosine triphosphate (ATP). The genetic components of SCZ are also shared with mitochondrial expression. 295 genes related to Schizophrenia that affect the structure and function of mitochondria were identified based on gene research [3]. Additionally, a study conducted by the genome-wide association studies (GWAS) located 22 genes out of the 295 on specific areas of the genome that have been linked to SCZ in other genetic studies [4]. Therefore, there's a possibility that the development of Schizophrenia and mitochondrial dysfunction may be interconnected. Unusual mitochondrial activity can be seen repeatedly in SCZ patients who experience psychosis [5]. Reports coming from phosphorus magnetic resonance studies (^{31}P -MRS) show there are lower levels of Adenosine triphosphate in the brains of patients with Schizophrenia. Furthermore, mitochondria in neural progenitors (the precursor cell that will develop into a neuron), cerebral organoids (lab-created tissue that mimics the brain), and cortical interneurons (a brain cell that regulates signaling between two neurons) obtained from pluripotent stem cells (iPSCs) of SCZ patients (iPSCs are cells repurposed to work like stem cells) display defects. On the other hand, the neural progenitors, cerebral organoids, and cortical interneurons derived from healthy individuals' iPSCs didn't have defective mitochondria [6]. Another disorder called 22q11 deletion disorder (22q11DS) also gives the individual having the condition a 30% chance of SCZ [10]. Both schizophrenia and 22q11DS patients have mitochondrial dysfunction. People having the genetic disorder, 22q11DS, interestingly have similar symptoms seen in schizophrenia, even if they do or don't develop schizophrenia. 22q11DS is a genetic disorder caused by a missing piece of genetic material located on chromosome 22 [12]. That's about 35 to 60 genes absent, of which six of them are involved in mitochondrial function. These genes are Prodh, Slc25a1, Mrpl40, Zdhhc8, Tiro, and Txnrd2 [8]. The similarities between the two

disorders lead the scientific community to suspect that 22q11DS's etiology may stem from abnormal mitochondrial function and problems in brain energy metabolism, which create schizophrenia-like symptoms. Many studies show mitochondrial dysfunction in people having 22q11 deletion disorder. For example, blood and plasma samples from children with the disorder are being tested to examine for signs of mitochondrial dysfunction [11]. Animal subjects also displayed the same results, 22q11DS was linked to mitochondrial malfunction; Improper mitochondrial gene expression in the prefrontal cortex (PFC) in particular [12]. A different study focused on animal models where genes Mrpl40 and Txnrd2 were absent and important for the presence of psychotic and cognitive symptoms in 22q11DS [14]. The research supports the possibility that mitochondrial dysfunction may contribute to the development of schizophrenia in 22q11DS patients. In conclusion, the findings indicate a notable correlation between mitochondrial dysfunction and schizophrenia symptoms. Mitochondria supply energy to cells, including astrocytes, whose vital roles for synaptic refinement are important for a normal functioning brain. Conversely, if mitochondrial pathways are not producing sufficient energy, this may result in altered astrocyte maturation and function.



Adapted from Farhy-Tselnicker and Nicola J. Allen, 2018 and from Schiweck et al., 2018

Astrocyte development and neuron interactions are key to understanding how disruptions in brain function contribute to schizophrenia [16].

Research Gaps in Dysfunction and Schizophrenia

Astrocyte activity is responsible for regulating the function and formation of synapses [16], helping build the brain blood barrier (BBB) and maintaining it [15], and preserving apt conditions in the brain (homeostasis) [16]. Although the progression of 22q11DS and schizophrenia from childhood to adulthood isn't fully understood because of the complexity of genetic and uncontrollable environmental factors, there's one area of the brain that doesn't fully develop until

later in life, the prefrontal cortex. The prefrontal cortex is responsible for decision-making, problem-solving, and controlling behavior and emotions. In SCZ, the PFC has structural and functional alterations, for instance, there are abnormal dendrites and fewer synapses, and some of these changes can be linked to mitochondrial dysfunction [16]. When astrocytes don't develop properly, it could cause the issues seen in the prefrontal cortex and cognitive problems as shown in 22q11DS and SCZ. Some genes absent in 22q11DS affect astrocyte maturation by negatively modifying mitochondria. The Prodh gene, for example, controls oxidative stress (maintains harmful free radicals and byproducts under control) that is present in astrocytes. Mice without Prodh have difficulty with sensorimotor skills. Moreover, the changing of the morphology (structure) and function of astrocytes has been shown to induce SCZ-related cognitive dysfunctions in rodents. Multiple studies have recognized recurring altered astrocyte makers like glial fibrillary acidic proteins (GFAP), aquaporin 4 (AQ-4), S100 β , glutaminase, thrombospondin (TSB-1), and excitatory amino acid transporter 2 (EAAT2). The support of modified astrocyte status in SCZ was first identified in postmortem studies. Although limited access to human-developing astrocytes in Schizophrenic patients has hindered the ability to conduct research, rodent experiments support how altered astrocytes may contribute to Schizophrenia.

Conclusion

To conclude, Schizophrenia is a complex neurodevelopmental disorder that involves structural and functional alterations in the brain, specifically in the prefrontal cortex, where decision-making and emotional regulation are disrupted. Mitochondrial dysfunction and impaired astrocyte activity are emerging as key contributors, influencing synaptic pruning, energy metabolism, and neural development. Continued research on the interconnected roles of astrocytes and mitochondria in brain disorders, such as SCZ and 22q11DS, may pave the way for improved understanding and more effective treatments.

References

- [1] Eroglu, C., & Barres, B. A. (2010). Regulation of synaptic connectivity by glia. *Nature*, 468(7321), 223–231. <https://doi.org/10.1038/nature09612> Retrieved: 12/5/24
- [2] Volz, H.-P., Riehemann, S., Maurer, I., Smesny, S., Sommer, M., Reinhard Rzanny, Holstein, W., Jörg Czekalla, & Sauer, H. (2000). Reduced phosphodiesters and high-energy phosphates in the frontal lobe of schizophrenic patients: a 31P chemical shift spectroscopic-imaging study. *Biological Psychiatry*, 47(11), 954–961. [https://doi.org/10.1016/s0006-3223\(00\)00235-3](https://doi.org/10.1016/s0006-3223(00)00235-3) Retrieved: 12/5/24
- [3] Eroglu, C., & Barres, B. A. (2010). Regulation of synaptic connectivity by glia. *Nature*, 468(7321), 223–231. <https://doi.org/10.1038/nature09612> Retrieved: 12/5/24
- [4] Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K., Holmans, P. A., Lee, P., Bulik-Sullivan, B., Collier, D. A., Huang, H., Pers, T. H., Agartz, I., Agerbo, E., Albus, M., Alexander, M., Amin, F., Bacanu, S. A., Begemann, M., Belliveau, R. A., ... O'Donovan, M. C. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, 511(7510), 421–427. <https://doi.org/10.1038/nature13505> Retrieved: 12/5/24
- [5] Regenold, W.T., et al. "Mitochondrial Detachment of Hexokinase 1 in Mood and Psychotic Disorders: Implications for Brain Energy Metabolism and Neurotrophic Signaling." *Journal of Psychiatric Research*, vol. 46, no. 1, Jan. 2012, pp. 95–104, <https://doi.org/10.1016/j.jpsychires.2011.09.018> Retrieved: 12/5/24
- [6] Brennand, K., et al. "Phenotypic Differences in iPSC NPCs Derived from Patients with Schizophrenia." *Molecular Psychiatry*, vol. 20, no. 3, 1 Apr. 2014, pp. 361–368, <https://doi.org/10.1038/mp.2014.22>. Retrieved: 12/5/24
- [7] Sun, Daqiang, et al. Large-Scale Mapping of Cortical Alterations in 22q11.2 Deletion Syndrome: Convergence with Idiopathic Psychosis and Effects of Deletion Size. *Vol.* 25, no. 8,

-
- 1 Aug. 2020, pp. 1822–1834,
<https://doi.org/10.1038/s41380-018-0078-5> Retrieved: 12/5/24
- [8] Prakash Devaraju, and Stanislav S Zakharenko. "Mitochondria in Complex Psychiatric Disorders: Lessons from Mouse Models of 22q11.2 Deletion Syndrome." *BioEssays*, vol. 39, no. 2, 3 Jan. 2017, <https://doi.org/10.1002/bies.201600177> Retrieved: 12/8/24
- [9] Chow, Eva W.C., et al. "Neurocognitive Profile in 22q11 Deletion Syndrome and Schizophrenia." *Schizophrenia Research*, vol. 87, no. 1-3, Oct. 2006, pp. 270–278, <https://doi.org/10.1016/j.schres.2006.04.007> Retrieved: 12/8/24
- [10] Chow, Eva W.C., et al. "Neurocognitive Profile in 22q11 Deletion Syndrome and Schizophrenia." *Schizophrenia Research*, vol. 87, no. 1-3, Oct. 2006, pp. 270–278, <https://doi.org/10.1016/j.schres.2006.04.007> Retrieved: 12/8/24
- [11] Napoli, Eleonora, et al. "Mitochondrial Citrate Transporter-Dependent Metabolic Signature in the 22q11.2 Deletion Syndrome." *Journal of Biological Chemistry*, vol. 290, no. 38, Sept. 2015, pp. 23240–23253, <https://doi.org/10.1074/jbc.m115.672360> Retrieved: 12/8/24
- [12] Stark, Kimberly L, et al. "Altered Brain MicroRNA Biogenesis Contributes to Phenotypic Deficits in a 22q11-Deletion Mouse Model." *Nature Genetics*, vol. 40, no. 6, 11 May 2008, pp. 751–760, <https://doi.org/10.1038/ng.138> Retrieved: 12/8/24
- [13] Chow, E. W. C., Watson, M., Young, D. A., & Bassett, A. S. (2006). Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. *Schizophrenia Research*, 87(1-3), 270–278. <https://doi.org/10.1016/j.schres.2006.04.007> Retrieved: 12/8/24
- [14] Fernandez, A., Meehan, D. W., Karpinski, B. A., Paronett, E. M., Bryan, C. A., Rutz, H. L., Radin, E. A., Lubin, N., Bonner, E. R., Popratiloff, A., Rothblat, L. A., Maynard, T. M., & LaMantia, A.-S. (2019). Mitochondrial Dysfunction Leads to Cortical Under-Connectivity and Cognitive Impairment. *Neuron*, 102(6), 1127-1142.e3. <https://doi.org/10.1016/j.neuron.2019.04.013> Retrieved: 12/8/24
- [15] Najjar, S., Pahlajani, S., De Sanctis, V., Stern, J. N. H., Najjar, A., & Chong, D. (2017). Neurovascular Unit Dysfunction and Blood–Brain Barrier Hyperpermeability Contribute to Schizophrenia Neurobiology: A Theoretical Integration of Clinical and Experimental Evidence. *Frontiers in Psychiatry*, 8. <https://doi.org/10.3389/fpsyg.2017.00083> Retrieved: 12/8/24
- [16] Notter, T. (2021). Astrocytes in schizophrenia. *Brain and Neuroscience Advances*, 5, 23982128211000148. <https://doi.org/10.1177/23982128211000148> Retrieved: 12/8/24

Direct correlation Between Sleep Deprivation and Parkinson's Disease Onset Through Glymphatic System Dysfunction

Arian Phillips

Abstract

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder caused by Alpha synuclein (ASYN) plaques and dopamine neuron loss. In PD, ASYN aggregates on synaptic vesicles creating plaques and disrupting cell function leading to disruptions in dopamine release. This loss of function in cells is known as neurodegeneration, the hallmark of PD. PD etiology is heterogeneous with multiple risk factors, the most notable is sleep disturbances. The relationship between PD and sleep is understated and overlooked especially as sleep deficiencies can directly lead to PD onset. Sleep deprivation directly leads to neurodegeneration, impairment of the brain's waste removal system, mitochondrial dysfunction, oxidative stress, as well as numerous genetic modifications responsible for modifying the risk factor and PD progression. After sleep loss, studies observed a decrease in ASYN proteins in CSF indicating it is being left on cellular material and not flushed out as it would under sufficient sleep. The role of sleep extends beyond merely a PD risk factor, sleep deprivation causes significant impairments in cognitive function, reduction in telomere length.

Introduction

Parkinson's disease (PD) is the most prevalent neurodegenerative disorder aside from Alzheimer's disease. All forms of PD are classified as an alpha-synucleinopathy derived from Alpha synuclein (ASYN) protein build up or aggregates. Synucleinopathies are a category of neurodegenerative diseases from ASYN plaques known as lewy bodies, responsible for PD pathology. In other words, ASYN protein accumulates on synaptic vesicles disrupting regular neuronal functions, causing neurodegeneration, and onset of various forms of PD. The classic, commonly seen, presentation of PD is known as Idiopathic or typical PD. The latter form of the illness, atypical PD, categorizes neurodegenerative diseases with similar symptoms but differences in pathophysiology. Atypical PD rather refers to parkinsonisms, not a diagnosis but a set of symptoms associated with PD but not specifically PD. Atypical PD includes known synucleinopathies such as multiple system atrophy and dementia with Lewy bodies. Additionally, atypical PD encompasses several diseases caused by tau protein aggregation referred to as tauopathies including Progressive Supranuclear Palsy and Corticobasal Degeneration. Undoubtedly, PD etiology is heterogeneous with many causes and risk factors. The most notable examined being sleep deprivation.

It is known that sleep deprivation holds profound effects on the human body such as numerous epigenetic, physiological, and neurological modifications featuring changes throughout the entirety of the human genome. Chronic sleep deprivation is directly correlated to an accelerated onset of Parkinson's disease (PD) along with an entire category of neurodegenerative disorders known as synucleinopathies. Alpha synuclein under normal sleep is removed via the brain's glymphatic waste removal system. Under a sufficient eight hours of sleep fluids are flushed across the brain washing it of any proteins in order to prevent accumulations or plaques. Under sleep disturbances or reductions the glymphatic system is disturbed and cannot operate properly; ASYN is not flushed out, it accumulates creating plaques. The plaque formations are known to cause neurodegeneration through disruption of functions on synaptic vesicles causing loss of function in neurons. Dopamine disruptions are another hallmark feature of PD where dopaminergic neurons are lost, decreasing dopamine levels and causing symptoms such as tremors and bradykinesia (slow movement). Oftentimes this dopaminergic neuron loss can be caused by the aggregation of ASYN on dopaminergic neurons. Nevertheless, The role of sleep deprivation in PD is profoundly underestimated and it should be noted that even a minor reduction from the recommended 8 hours of sleep can directly contribute to PD onset.

The Profound Negative Effects of Deficient Sleep

One third of adults and 70% of teenagers receive less than the recommended 8 hours of sleep indicating prevalence and importance of an issue such as sleep deprivation [16]. According to UC Berkeley Neuroscience professor Matthew Walker, the state of wakefulness can be described as "low-level brain damage" and at least 8 hours of sleep is necessary to repair your brain. Without this 8 hours of consistent sleep numerous physiological and neurological changes occur. Adults above the age of 60 missing less than 1% of deep sleep yearly, increases risks of dementia by 27% [9]. Modifications observed in not just the elderly age group include a 200% increased risk in heart attacks. Further on daylight savings time in spring where sleep is lost by 1 hour a subsequent 24% increase in heart attacks that occur on that day; whereas in the fall where an hour of sleep is gained a 21% reduction in heart attacks is observed, this trend is even observed in suicide rates and car accidents [19].

Sleep disturbances heavily influence epigenetics; Epigenetics refers to the interplay between the environment and gene expressions. A major component of epigenetics, DNA methylation, refers to the removal or addition of methyl groups (CH_3) onto DNA nucleotides influencing the strength at which a gene is expressed. A study performed on mice displayed DNA methylation was affected in 227 instances, among the most notable was a change in the expression of a gene, Dlg 4, that led to autism-like symptoms [12]. Sleep loss in one night alone led to "148 significant differentially methylated regions (DMRs) in subcutaneous adipose tissue". 92 of these DMRs were hypermethylated and held connections to DNA damage and lipid metabolism. Of these genes a few were linked to Adipogenesis, accumulation of adipose or fat tissue [4]. Additionally, Sleep deprivation has links to telomere length reduction. Telomeres, refer to repeating, noncoding, sequences of nucleotides that correlate to biological age, the longer the repeating sequence of bases represents the younger age, and shorter sequences are representative of older age. Decrease in telomere length has been linked with inflammation, chronic stress, hostility and even lower

socioeconomic statuses. A study completed on 434 participants observed that men who received 5 or fewer hours of sleep had telomeres averaging 6 percent shorter in length compared to those who slept greater than 7 hours.[ii]. In other words, the sleep deprived men experienced more biological aging than those who slept sufficiently. There is a bidirectional relationship between sleep decline and aging. As people their amount of sleep also declines and that is paired with the decrease in telomere length that subsequently causes aging. It is important to note, these changes are not coincidental [19].

Sleep deprivation is directly linked to neurodegeneration and therefore several neurodegenerative diseases. Neurodegeneration can be described as the progressive loss of structure and therefore function of neurons in the central and peripheral nervous systems. Studies have shown that loss of Rapid Eye Movement (REM) sleep directly causes neurodegeneration. Under REM sleep loss the noradrenaline neurotransmitter levels increase causing neuronal damage and cell apoptosis or death. Under a sufficient 8 hours of sleep noradrenaline levels remain at a healthy dose functioning to protect neurons, allow for proper memory consolidation and correctly facilitate synaptogenesis formation of new synapses [7]. REM sleep deprivation also causes glymphatic system dysfunction allowing for accumulation of amyloid β_{42} and phosphorylated tau proteins which are directly linked to Alzheimer's disease and neuronal damage ie: neurodegeneration. It also causes mitochondrial dysmorphism and a subsequent cease or decline of cellular energy production ATP promoting apoptosis [7]. Simply stated loss of sleep destroys neurons.

Memory consolidation issues presented by REM sleep loss can further be attributed to changes in the Hippocampal CA1 region. Muscarinic, a subtype of acetylcholine receptors regulates glutamate release responsible for shaping learning, and memory consolidation. The Cholinergic System as described above is dependent upon this process of glutamate release for proper memory and learning. REM sleep deprivation leads to harmful modification in the CA1 Cholinergic Muscarinic receptors that lead to memory deficit and learning difficulties known as REM sleep deprivation Amnesia [7]

Direct Trend Between Sleep Loss and PD

Before it is stated that sleep deprivation has a direct correlation to PD, the mechanisms in which the condition operates must be defined. It is commonly known that PD is directly associated with a loss of Dopaminergic neurons located in the brain's substantia nigra region responsible for motor control. Reduction in dopamine production is the cause of PD symptoms including tremors and bradykinesia . Yet another major cause of PD is attributed to the 140 amino acid protein Alpha synuclein (ASYN). ASYN falls in a category of three poorly understood proteins known as synucleins. ASYN however is the most understood protein of the group and coded specifically by the SNCA gene located on chromosome 4. The protein exclusively occurs on central nervous system (CNS) neurons on the presynaptic vesicles responsible for tasks related to neurotransmitter release. When alpha synuclein protein misfolds either from genetic variations, or environmental factors, it aggregates forming of plaques called Lewy bodies that disrupt its tasks on the synaptic vesicles.

A study performed on transgenic mice, modified to exhibit human-like genes, observed dopaminergic neurons of the substantia nigra (SN) region and ASYN, revealed a progressive loss of

dopaminergic neuron loss in SN increasing from 9 to 20 months along with an age-related decline in motor function [22]. Further intracellular dangers of Lewy bodies were outlined in a study observing Neuronal Cell death in PD where it was found that Lewy bodies were associated with mitochondrial and nuclear degradation. This contributes to a decrease in cellular energy and axonal transport. Additionally interactions between ASYN and DNA are observed indicating that epigenetic changes may have occurred [17]. After the results it can be concluded that Lewy bodies are considered cytotoxic; the plaques are detrimental to the wellbeing of the cell causing cell death.

A study on 536 participants was conducted to determine a correlation between sleep characteristics and ASYN protein levels. The study concluded that lower levels of ASYN found in cerebrospinal spinal fluid (CSF) were associated with those who slept for too few hours, as well as an excess amount of hours. It was later stated that those who slept excessively or for too few hours did not receive the quality of uninterrupted sleep as those who slept around 8 hours as recommended; therefore the study concluded that those who slept 8 hours had lower levels of CSF ASYN [21]. It is important to note that lower levels of ASYN in CSF indicate glymphatic system dysfunction and higher levels of ASYN are being left on neuronal synaptic vesicles and aggregating. The study suggests that this trend may directly correlate to the onset of Neurodegenerative disorders, specifically synucleinopathies characterized by Lewy body pathologies. Additionally it was stated that interruptions during sleep reduce sleep quality and may lower CSF ASYN levels. Those who work Night shifts also had lower levels of CSF ASYN [21].

Sleep loss is very frequently observed in those with PD. 80% of patients experience poor quality sleep: fragmented sleep, REM sleep reduction and increased sleep latency. REM sleep behavior disorder (RBD) is known as a prodromal symptom, indicative of PD onset and associated with up to 60% of cases. RBD disrupts REM sleep where affected individuals physically act out dreams [7]. The onset of RBD caused by PD further accelerates the disease through sleep reductions. Many PD

PD causes a depolarization in astrocyte cell membrane aquaporin, Aquaporin 4 (AQP4). AQP4 depolarization leads to an uneven concentration of ions across the cell membrane impairing the flow of CSF through cellular material and therefore disruption of the glymphatic system. [15]. A notable three way bidirectional relationship between sleep, glymphatic system and PD. Sleep disturbances function as a risk factor and a symptom of PD. Glymphatic system dysregulation causes PD; PD can cause loss of sleep and therefore glymphatic dysfunction. Sleep deprivation can cause glymphatic system dysfunction and vice versa [15]. *Figure 1* illustrates the relationship.

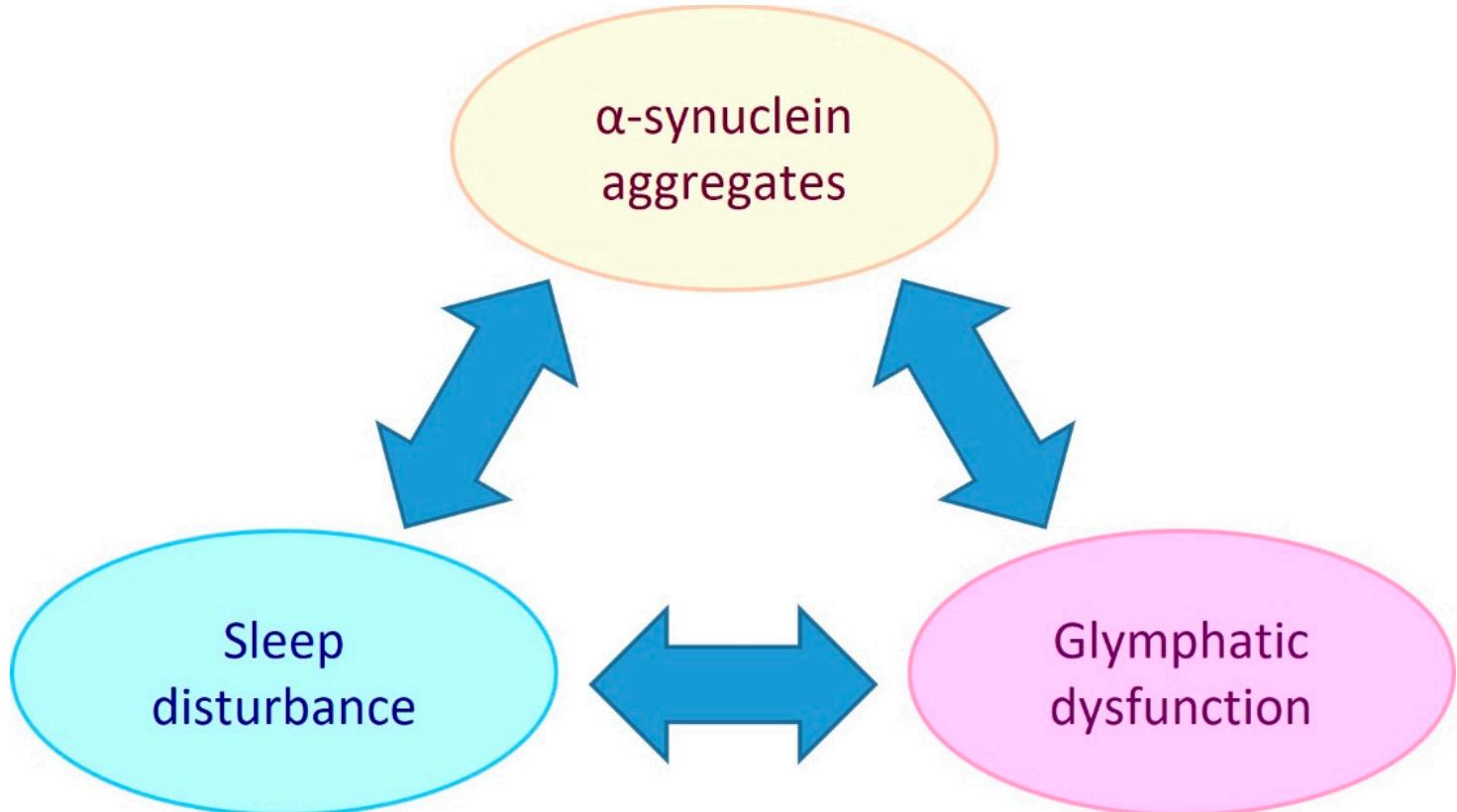


Figure 1

Oxidative stress functions as another major mechanism underlying neurodegeneration. Oxidative stress occurs when reactive oxygen species (ROS) is produced in excess via environmental factors during mitochondrial ATP synthesis. ROS is a free radical, or unstable atom with an unstable single electron in the outer orbital. These free electrons attack and steal electrons from other atoms or molecules causing a cascade of events ending in mitochondrial dysfunction and subsequent cell death. When oxidative stress in neurons occurs causing loss of function, it is described as neurodegeneration -the hallmark of PD. [8]

Sleep deprivation not only causes neurodegeneration through Lewy body formations but also oxidative stress. A study performed on fruit flies observed a bidirectional relationship between sleep deprivation and oxidative stress. The study revealed that sleep is required in order to have oxidative stress resilience. In other words, fruit flies that experienced decreased sleep were more susceptible to oxidative stress and ROS accumulation. Sleep is imperative for ROS clearance, and sufficient sleep must occur for proper clearance. This idea was defended as it was observed that increased sleep promoted oxidative stress resistance. ROS holds an important role in sleep cycles, it was observed that decreased ROS led to decreased sleep as less had to be cleared out. Moreover, greater amounts of ROS reflect a greater need for sleep highlighting the importance of sufficient sleep [8].

Finally, Epigenetic components causing PD onset include the activation and overexpression of BDNF gene on chromosome 11. BDNF is responsible for coding a protein called

brain-derived neurotrophic (BDNF) that plays a crucial role in Neuron Survival, Neuronal Growth and Synaptic plasticity [5]. BDNF is a neurotrophic factor meaning it functions to maintain neurons. A study completed on rats indicated an increase in BDNF expression can occur under only 6 hours of sleep deprivation [13]. Overexpression of the BDNF gene can cause loss of function leading to neuronal death often in dopaminergic neurons.

Extenuating Circumstances

While the relationship between sleep deprivation, epigenetic alterations, in PD has been extensively studied, it is very important to understand the broader context in which the research is conducted, several extenuating circumstances such as, methodological limitations, biases, and study sample populations can influence research findings. Analyzing the studies in which the results are gathered is essential to producing accurate and meaningful results.

The majority of sleep studies were conducted on men. This trend was prevalent in scientific research where biological differences in women were neglected and they were seen as “smaller men” and lacked research up until late 20th century. However, to this date, several studies regarding sleep fail to hold an inclusive sample size and potentially underestimate the effects of sleep deprivation on women specifically. For instance, Differences in sleep disorder presentations based on sex following adolescence were observed in a study. It was observed that women showed higher rates of insomnia and restless leg syndrome due to their reproductive hormonal shifts as well as lower rates of sleep breathing disorder compared to men [18]. Another study outlined the importance of including both sexes in preclinical sleep studies and analyses. It was argued that there is limited clinical data on sleep function between genders despite greater efforts being made to fill in such gaps. Further, only a few studies have accounted for differences in sexes during sleep studies thus, failing to account for large biological differences leading to confounded and flawed results. Additionally the study completed on mice suggested that females exhibited more total REM sleep aligning with another study suggesting women need more sleep than men and are more susceptible to sleep disturbances. The mechanisms that underlie this are unknown and further defends the idea that women are understudied in the field of sleep.

Researching sleep leads to several ethical concerns limiting further data. Profound consequences of sleep deprivation have undoubtedly been revealed. Ethically testing how complete sleep deprivation, or even longer term cases are difficult to ethically test. Incorporating human test subjects into such experiments is very difficult to do. Studies completed on those who already experience sleep deprivation for lifestyle or career choices are more achievable, however long term research is difficult to carry out. Test subjects that experience sleep deprivation to begin with may also have present, possibly unknown, comorbidities contributing to sleeping difficulties. These underlying causes such as insomnia, anxiety, or bi polar disorder have a likelihood of influencing study results.

Regardless of research biases and inefficiencies, sleep deprivation is undoubtedly an epidemic. One third of adults and 70% of teenagers receive less than the recommended 8 hours. The American lifestyle does not function as a conducive environment to receive 8 hours of sleep. This trend is specifically prevalent in high school students who have a delayed circadian rhythm leading to late sleep. But as schools start at 8 am they are forced to wake at early hours to attend school. The

setup of high schools and 9-5 jobs make it difficult for people to get a complete 8 hours of sleep to repair the negative effects of wakefulness. Students in particular need 8 hours of sleep to enhance learning efficiency and comprehension. Even shorter school days but paired greater sleep quality will enhance the quality of our education as students today are largely sleep deprived and cognitively impaired. The majority of the US population suffers from insufficient sleep not only rooted from the setup of our lifestyle but also from inadequate knowledge regarding the negative effects. Revamping the setup of life so that people can receive greater sleep is unrealistic and will not occur. However, the way sleep is seen among people can be altered

In conclusion, Sleep deprivation holds numerous consequences extending far beyond mere fatigue. Sleep deprivation is heavily overlooked by the general public and should be taken seriously. Loss of sleep causes numerous intracellular effects including impairment of the brain's glymphatic waste removal system allowing for accumulation of ASYN and phosphorylated tau proteins to deposit on presynaptic neurons disrupting cell function and causing neurodegeneration. Mitochondrial loss was also reported inhibiting ATP synthesis leading to energy loss. Other non cellular changes include severe cognitive decline, 200% increases in heart rate risks, 70% decline in killer immune cells, and direct aging via telomere shortening. Sleep deprivation is not only a byproduct of modern life, rather an extremely prevalent and pervasive epidemic that must be studied further with publicized results so that more people can avoid the negative consequences.

References

- [1] Andersen, Monica L., et al. (2023). Sleep in women: a narrative review of hormonal influences, sex differences and health implications. *Frontiers in Sleep*, 2. <https://doi.org/10.3389/frsle.2023.1271827>
- [2] Bendor, Jacob T., et al. (2013). The Function of α -Synuclein. *Neuron*, 79(6), 1044–1066. <https://doi.org/10.1016/j.neuron.2013.09.004>
- [3] Bollu, Pradeep C., et al. (2017). Sleep and Parkinson Disease. *Missouri Medicine*, 114(5), 381. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6140184/>
- [4] Cedernaes, Jonathan, et al. (2018). Acute sleep loss results in tissue-specific alterations in genome-wide DNA methylation state and metabolic fuel utilization in humans. *Science Advances*, 4(8), eaar8590. <https://doi.org/10.1126/sciadv.aar8590>
- [5] OMIM. (2016). *113505 - BRAIN-DERIVED NEUROTROPHIC FACTOR; BDNF. Omim.org. <https://omim.org/entry/113505?search=BDNF&highlight=bdnf>
- [6] Gaine, Meghan E., et al. (2018). Sleep Deprivation and the Epigenome. *Frontiers in Neural Circuits*, 12(14). <https://doi.org/10.3389/fncir.2018.00014>
- [7] Giri, Santosh, et al. (2023). REM Sleep Loss-Induced Elevated Noradrenaline Plays a Significant Role in Neurodegeneration: Synthesis of Findings to Propose a Possible Mechanism of Action from Molecule to Patho-Physiological Changes. *Brain Sciences*, 14(1), 8. <https://doi.org/10.3390/brainsci14010008>
- [8] Hill, Vanessa M., et al. (2018). A bidirectional relationship between sleep and oxidative stress in Drosophila. *PLOS Biology*, 16(7), e2005206. <https://doi.org/10.1371/journal.pbio.2005206>
- [9] Himali, Jayandra J., et al. (2023). Association Between Slow-Wave Sleep Loss and Incident Dementia. *JAMA Neurology*, 80(12). <https://doi.org/10.1001/jamaneurol.2023.3889>
- [10] Hwang, Onyou. (2013). Role of Oxidative Stress in Parkinson's Disease. *Experimental Neurobiology*, 22(1), 11. <https://doi.org/10.5607/en.2013.22.1.11>
- [11] Jackowska, Marta, et al. (2012). Short Sleep Duration Is Associated with Shorter Telomere Length in Healthy Men: Findings from the Whitehall II Cohort Study. *PLoS ONE*, 7(10), e47292. <https://doi.org/10.1371/journal.pone.0047292>
- [12] Lahtinen, Annamari, et al. (2019). A distinctive DNA methylation pattern in insufficient sleep. *Scientific Reports*, 9(1). <https://doi.org/10.1038/s41598-018-38009-o>
- [13] Ma, Ting, et al. (2020). Activation of brain-derived neurotrophic factor signaling in the basal forebrain reverses

-
- acute sleep deprivation-induced fear memory impairments. *Brain and Behavior*, 10(4). <https://doi.org/10.1002/brb3.1592>
- [14] Mannino, George S., et al. (2024). The importance of including both sexes in preclinical sleep studies and analyses. *Scientific Reports*, 14(1). <https://doi.org/10.1038/s41598-024-70996-1>
- [15] Massey, Anthony, et al. (2022). Glymphatic System Dysfunction and Sleep Disturbance May Contribute to the Pathogenesis and Progression of Parkinson's Disease. *International Journal of Molecular Sciences*, 23(21), 12928. <https://doi.org/10.3390/ijms232112928>
- [16] Miguez, Maria J., et al. (2020). Disparities in Sleep Health among Adolescents: The Role of Sex, Age, and Migration. *Sleep Disorders*, 1–6. <https://doi.org/10.1155/2020/5316364>
- [17] Power, John H. T., et al. (2016). Lewy Bodies and the Mechanisms of Neuronal Cell Death in Parkinson's Disease and Dementia with Lewy Bodies. *Brain Pathology*, 27(1), 3–12. <https://doi.org/10.1111/bpa.12344>
- [18] Tobias, Lee, et al. (2021). Impact of Sex on Sleep Disorders Across the Lifespan. *Clinics in Chest Medicine*, 42(3), 427–442. <https://doi.org/10.1016/j.ccm.2021.04.005>
- [19] Walker, M. P. (2017). *Why We Sleep: Unlocking the Power of Sleep and Dreams*. Scribner, An Imprint Of Simon & Schuster, Inc.
- [20] Wang, Chun S., et al. (2022). BDNF signaling in context: From synaptic regulation to psychiatric disorders. *Cell*, 185(1), 62–76. <https://doi.org/10.1016/j.cell.2021.12.003>
- [21] Wang, Xin, et al. (2020). Associations of sleep characteristics with alpha-synuclein in cerebrospinal fluid in older adults. *Annals of Clinical and Translational Neurology*, 7(10), 2026–2034. <https://doi.org/10.1002/acn3.51204>
- [22] Wegrzynowicz, Magdalena, et al. (2019). Depopulation of dense α -synuclein aggregates is associated with rescue of dopamine neuron dysfunction and death in a new Parkinson's disease model. *Acta Neuropathologica*, 138(4), 575–595. <https://doi.org/10.1007/s00401-019-02023-x>

Unraveling the Link: Smoking as a Modifiable Risk Factor for Dementia

Prakhar Singhania

Abstract

Dementia, a progressive neurological disorder, affects over 55 million individuals globally, with this figure projected to double by 2050. Smoking, a significant modifiable risk factor, has been extensively linked to increased dementia risk through mechanisms involving oxidative stress, inflammation, and vascular dysfunction. This literature review synthesizes current evidence on the relationship between smoking and dementia, with a focus on epidemiological findings, molecular mechanisms, neuroimaging outcomes, and the benefits of smoking cessation. Epidemiological studies reveal that current smokers face a 30-40% higher risk of developing dementia compared to non-smokers, with smoking accounting for approximately 14% of global dementia cases. Molecular research highlights that smoking exacerbates amyloid- β aggregation, tau hyperphosphorylation, and mitochondrial dysfunction, accelerating neurodegenerative processes. Neuroimaging studies corroborate these findings, showing significant reductions in gray matter volume and hypoperfusion in smokers. Importantly, smoking cessation demonstrates the potential to mitigate these risks, with evidence of partial recovery in cortical thickness and improved cognitive outcomes within 5-10 years of quitting. The review underscores the critical role of public health strategies in integrating smoking cessation programs to reduce dementia prevalence. Policymakers should prioritize education, genetic screening for high-risk populations, and access to cessation resources. Future research must explore the long-term cognitive benefits of cessation and innovative interventions, such as pharmacogenetic therapies. By addressing smoking as a preventable risk factor, healthcare systems can significantly alleviate the global dementia burden and improve quality of life for at-risk populations.

Introduction

Dementia is a progressive neurological disorder characterized by cognitive decline severe enough to impair daily functioning. Currently, over 55 million individuals live with dementia worldwide, with projections indicating this number will double by 2050 due to aging populations and lifestyle changes [1][2]. Alzheimer's disease (AD) and vascular dementia (VaD) are the most prevalent forms, collectively accounting for the majority of cases. These disorders not only impact individuals and families but also impose substantial socioeconomic burdens on healthcare systems globally [3].

Smoking, a major modifiable risk factor, has been extensively linked to an increased risk of dementia. Smokers experience heightened rates of oxidative stress, systemic inflammation, and vascular dysfunction, all of which are key contributors to cognitive decline and neurodegeneration [4][5]. Epidemiological studies reveal that current smokers are 30-40% more likely to develop

dementia compared to non-smokers, with smoking intensity and duration exacerbating these risks [6][7]. Moreover, smoking interacts with genetic factors, such as the APOE ε4 allele, which further amplifies its detrimental effects on brain health [8][9].

The mechanisms by which smoking contributes to dementia are multifaceted. Nicotine and other components of cigarette smoke directly damage neuronal membranes and promote the accumulation of amyloid-β and tau proteins—hallmarks of AD pathology [10][11]. Concurrently, smoking-induced vascular damage accelerates brain aging by impairing cerebral perfusion, leading to chronic hypoxia and atrophy of brain regions critical for memory and cognition, such as the hippocampus and prefrontal cortex [12][13].

In addition to its direct effects, smoking compounds the risks associated with other modifiable factors, such as poor diet, physical inactivity, and excessive alcohol consumption. These synergistic effects highlight the importance of adopting comprehensive lifestyle interventions for dementia prevention [14][15]. Understanding smoking's role in dementia pathogenesis is critical for informing public health policies and clinical strategies aimed at reducing the global dementia burden.

This review synthesizes current evidence on the relationship between smoking and dementia, with a focus on epidemiological findings, biological mechanisms, and the benefits of smoking cessation. It also explores the interaction between smoking and genetic predispositions, emphasizing the need for targeted interventions to mitigate this preventable risk factor.

Methods

A comprehensive and systematic approach was used to review the available literature on smoking and dementia. The methodology was designed to ensure the inclusion of high-quality, peer-reviewed studies while addressing various dimensions of the relationship between smoking and dementia as shown in figure 1.

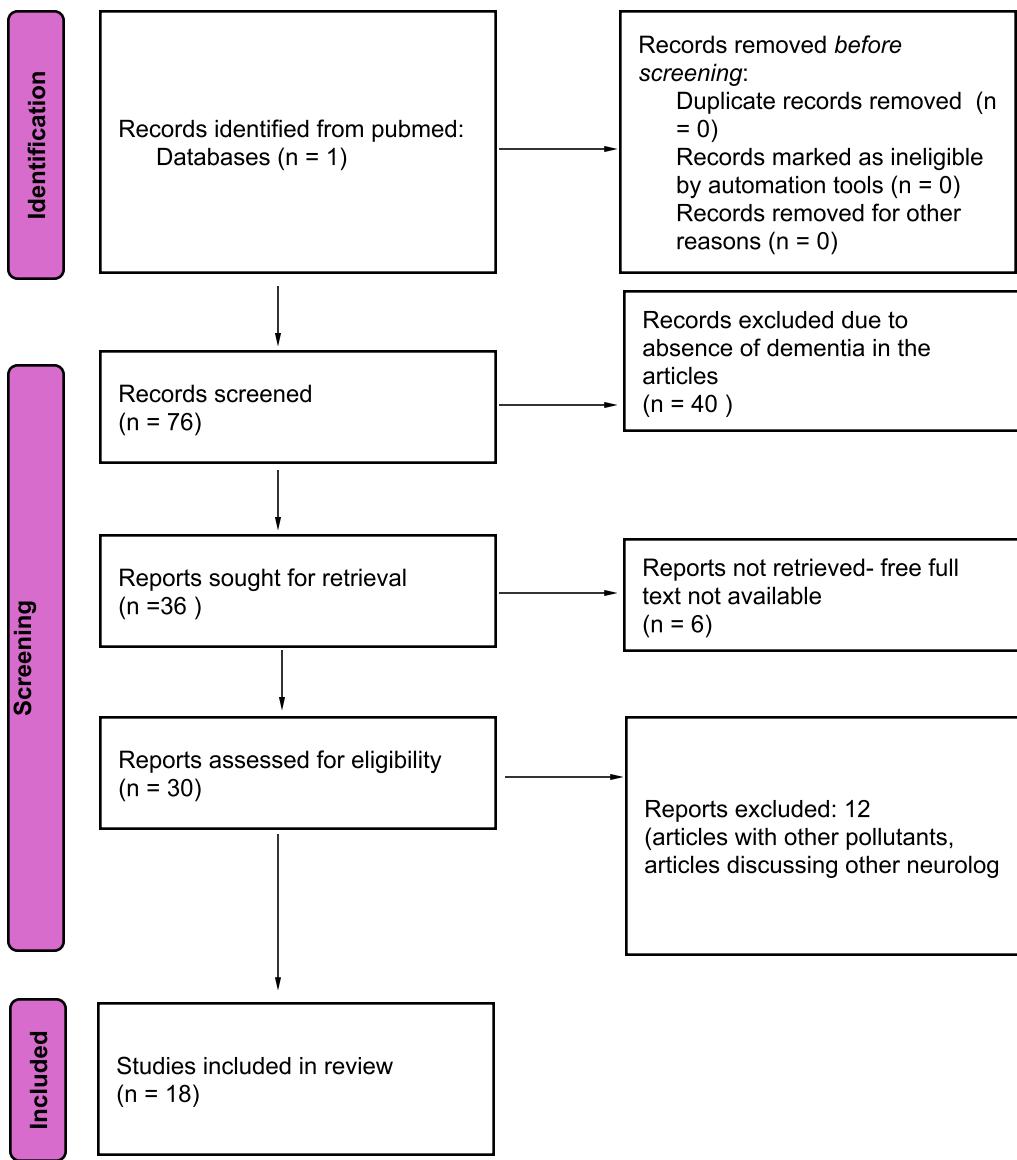


Figure 1. Flow diagram showing the method of literature review and how articles are chosen

PubMed was searched for studies published between 2014-2024. Keywords included "smoking," "dementia," "cognitive decline," "Alzheimer's Disease," and "vascular dementia."

Inclusion Criteria: Research examining smoking's impact on cognitive impairment, brain structure, biomarkers of AD, or dementia risk. Both human and animal studies with translational relevance, detailed methodologies, and robust statistical analyses were considered. Studies utilizing neuroimaging techniques, such as MRI and PET scans, to evaluate brain changes were prioritized.

Exclusion Criteria: Reviews lacking quantitative analysis, studies funded by entities with conflicts of interest (e.g., tobacco industry sponsorship), and articles unrelated to dementia risk were excluded. Additionally, studies with small sample sizes or insufficient controls for confounding variables were omitted.

Findings were integrated to identify patterns, inconsistencies, and gaps in the literature. A narrative synthesis was conducted to contextualize the quantitative data within broader biological and public health frameworks.

This rigorous methodological framework allowed for a comprehensive examination of smoking's role in dementia pathogenesis and provided a foundation for evidence-based conclusions and recommendations.

Results

Epidemiological Evidence: Numerous cohort studies confirm that smoking increases dementia risk. Current smokers exhibit a 30-40% higher risk of developing dementia than non-smokers, with meta-analyses reporting relative risks ranging from 1.3 to 1.6 [4][6][7]. Population-based studies estimate that approximately 14% of all dementia cases worldwide are attributable to smoking, highlighting the substantial public health impact of this modifiable risk factor [9][14]. Former smokers demonstrate reduced but still elevated risks, suggesting partial reversibility of smoking's harmful effects [9][17].

Molecular Mechanisms: Smoking exacerbates oxidative stress, inflammation, and vascular damage, contributing to cognitive decline. Chronic oxidative stress damages neuronal membranes and disrupts mitochondrial function, while inflammation increases cytokine production, accelerating neurodegeneration [5][10][17]. Nicotine and other cigarette smoke components, including polycyclic aromatic hydrocarbons (PAHs) and heavy metals, facilitate amyloid- β aggregation and tau protein hyperphosphorylation—key pathological features of AD [6][11][12]. Furthermore, smoking-induced vascular dysfunction reduces cerebral perfusion and impairs glucose metabolism in critical brain regions, such as the hippocampus and prefrontal cortex [11][13][16].

Neuroimaging Findings: Neuroimaging studies provide robust evidence of smoking-related structural brain changes. Chronic smokers exhibit significant reductions in gray matter volume in the prefrontal cortex, hippocampus, and entorhinal cortex, regions critical for memory and executive function [6][13][18]. Longitudinal analyses demonstrate that smokers experience 5-10% greater brain volume loss over time compared to non-smokers, with these changes correlating strongly with cognitive decline [7][14][15]. Functional imaging studies reveal reduced cerebral blood flow and hypoperfusion in smokers, aligning with vascular dementia pathophysiology [12][16]. Additionally, smokers show elevated amyloid plaque burden and tau deposition on PET imaging, further linking smoking to AD-specific changes [11][18].

Impact of Smoking Cessation: Cessation significantly reduces dementia risk, with former smokers demonstrating a 20-30% lower risk compared to current smokers. Neuroimaging studies highlight partial recovery of cortical thickness and improved cerebral perfusion within 5-10 years of quitting [15][18]. Longitudinal data indicate that individuals who quit smoking exhibit slower rates of cognitive decline and reduced oxidative stress levels compared to those who continue smoking [9][16][17]. Importantly, the benefits of cessation are most pronounced in individuals who quit earlier in life, underscoring the value of early intervention [14][18].

Discussion

Mechanisms of Neurodegeneration: Smoking-induced oxidative stress and inflammation emerge as primary drivers of neuronal damage. Oxidative stress accelerates lipid peroxidation and protein dysfunction, impairing mitochondrial activity and leading to neuronal apoptosis [5][12][15]. Inflammatory responses triggered by smoking increase cytokine levels, which exacerbate blood-brain barrier disruption and further contribute to neurodegenerative processes [10][16]. Vascular dysfunction resulting from smoking also leads to hypoxia and chronic cerebral hypoperfusion, which are associated with greater brain atrophy and cognitive impairment [11][13][18].

Interaction with Genetic Risk Factors: The interaction between smoking and genetic predispositions, such as the APOE ε4 allele, underscores a compounded risk for dementia. APOE ε4 carriers who smoke exhibit heightened amyloid-β deposition and glucose hypometabolism in the brain, exacerbating cognitive decline and increasing the risk of AD [8][14][17]. This interplay highlights the importance of genetic screening and targeted interventions for high-risk individuals.

Reversibility of Smoking Damage: Evidence suggests that smoking cessation mitigates many risks associated with dementia. Former smokers show improvements in cerebral perfusion, reduced markers of oxidative stress, and partial recovery in cortical thickness over time [15][18]. These neuroplastic changes, though significant, are influenced by the duration and intensity of prior smoking exposure, emphasizing the need for early intervention [9][16]. Additionally, cessation has been associated with slower cognitive decline and a reduced risk of AD and VaD, supporting its role as a key preventative strategy [10][13][18].

Public Health Implications: The public health burden of smoking-related dementia underscores the urgency of implementing comprehensive cessation programs. Integrating smoking cessation initiatives with education on dementia prevention could enhance awareness and reduce prevalence rates [7][16]. Policymakers should prioritize accessible resources for smoking cessation, such as counseling and pharmacological aids, particularly for middle-aged populations at heightened risk of developing dementia [6][15]. Furthermore, longitudinal research is needed to explore the long-term cognitive benefits of cessation and to develop targeted interventions for populations with overlapping risk factors.

Conclusion

Smoking is a significant yet modifiable risk factor for dementia, with robust evidence linking it to oxidative stress, inflammation, vascular damage, and structural brain changes. These mechanisms underscore the profound impact of smoking on cognitive decline, particularly when compounded by genetic predispositions such as the APOE ε4 allele. Importantly, the risk is not irreversible. Smoking cessation has demonstrated clear benefits, including partial recovery of cerebral perfusion, reduced oxidative stress, and a slower rate of cognitive decline, particularly when implemented early in life.

The findings of this review emphasize the critical importance of integrating smoking cessation into public health strategies aimed at dementia prevention. Comprehensive policies must prioritize education, access to cessation resources, and targeted interventions for high-risk populations. Moreover, future research should explore pharmacogenetic therapies and other innovative approaches to mitigate the long-term risks associated with smoking and dementia. By addressing smoking as a preventable risk factor, healthcare systems can take a proactive stance in reducing the global burden of dementia. This approach not only has the potential to improve individual outcomes but also to alleviate the socioeconomic pressures associated with this devastating condition.

Glossary

Alzheimer's disease- Alzheimer's disease is the biological process that begins with the appearance of a buildup of proteins in the form of amyloid plaques in the brain. This causes brain cells to die over time and the brain to shrink.

Vascular dementia- Vascular dementia is a general term describing problems with reasoning, planning, judgment, memory and other thought processes caused by brain damage from impaired blood flow to the brain.

Oxidative stress- Oxidative stress is an imbalance between free radicals and antioxidants. There is excess of free radicals which harm body's cells and tissues.

Lipid peroxidation- Lipid peroxidation is a complex chemical process that leads to oxidative degradation of lipids, resulting in the formation of peroxide and hydroperoxide derivatives which are harmful to cells.

Apoptosis- death of a cell

Cytokine- Cytokines are small proteins important in cell signaling

Prefrontal cortex- It covers the front part of the frontal lobe of the cerebral cortex (brain).

Hippocampus- The hippocampus is part of the limbic system, and plays important roles in the consolidation of information from short-term memory to long-term memory, and in spatial memory that enables navigation.

Entorhinal cortex- It located in the medial temporal lobe, whose functions include being a widespread network hub for memory, navigation, and the perception of time.

Amyloid plaque- It is an extracellular deposit of amyloid beta (Aβ) protein that is present in abundance in degenerated grey matter of the brain.

tau deposition- The deposition of abnormal tau protein is characteristic of Alzheimer's disease

PET imaging- A positron emission tomography (PET) scan is an imaging test that can help reveal the metabolic or biochemical function of your tissues and organs.

References

- [1] Almahasneh, Fatimah et al. (2024). Nicotine Abuse and Neurodegeneration: Novel Pharmacogenetic Targets to Aid Quitting and Reduce the Risk of Dementia. *CNS & Neurological Disorders- Drug Targets.* 23(1):2-8. doi:10.2174/1871527322666230220121655. Retrieved: 07/01/2025.
- [2] Durazzo, Timothy et al. (2015). Comparison of Regional Brain Perfusion Levels in Chronically Smoking and Non-Smoking Adults. *International Journal of Environmental Research and Public Health.* 12:8198-8213. doi:10.3390/ijerph120708198. Retrieved: 07/01/2025.
- [3] Karama, S. et al. (2015). Cigarette Smoking and Thinning of the Brain's Cortex. *Molecular Psychiatry.* 20(6):778-785. doi:10.1038/mp.2014.187. Retrieved: 07/01/2025.
- [4] Durazzo, Timothy et al. (2014). Smoking and Increased Alzheimer's Disease Risk: A Review of Potential Mechanisms. *Alzheimers Dementia.* 10(3 Suppl):S122-S145. doi:10.1016/j.jalz.2014.04.009. Retrieved: 07/01/2025.
- [5] Calderón-Garcidueñas, Lilian et al. (2016). Smoking and Cerebral Oxidative Stress and Air Pollution: A Dreadful Equation with Particulate Matter Involved and One More Powerful Reason Not to Smoke Anything!. *Journal of Alzheimer's Disease.* 54(1):109-112. doi:10.3233/JAD-160510. Retrieved: 07/01/2025.
- [6] Durazzo, Timothy et al. (01/11/2018). Cigarette Smoking is Associated with Cortical Thinning in Anterior Frontal Regions, Insula and Regions Showing Atrophy in Early Alzheimer's Disease. *Drug Alcohol Dependence.* 192:277-284. doi:10.1016/j.drugalcdep.2018.08.009. Retrieved: 07/01/2025.
- [7] Deal, Jennifer A. et al. (2020). Relationship of Cigarette Smoking and Time of Quitting with Incident Dementia and Cognitive Decline. *Journal of the American Geriatrics Society.* 68(2):337-345. doi:10.1111/jgs.16228. Retrieved: 07/01/2025.
- [8] Durazzo, Timothy et al. (2014). Smoking and Increased Alzheimer's Disease Risk: A Review of Potential Mechanisms. *Alzheimers Dementia.* 10(3 Suppl):S122-S145. doi:10.1016/j.jalz.2014.04.009. Retrieved: 07/01/2025.
- [9] Chen, Mayun et al. (12/02/2021). A History of Cigarette Smoking is Associated with Faster Functional Decline and Reduction of Entorhinal Cortex Volume in Mild Cognitive Impairment. *Aging.* 13(4):6205-6213. <https://doi.org/10.18632/aging.202646>. Retrieved: 07/01/2025.
- [10] Whitsel, Nathan et al. (2022). Long-term Associations of Cigarette Smoking in Early Mid-life with Predicted Brain Aging from Mid- to Late Life. *Addiction.* 117(4):1049-1059. doi:10.1111/add.15710. Retrieved: 07/01/2025.
- [11] Elbejjani, Martine et al. (2019). Cigarette Smoking and Gray Matter Brain Volumes in Middle Age Adults: The CARDIA Brain MRI Sub-study. *Translational Psychiatry.* 9(1):78. doi:10.1038/s41398-019-0401-1. Retrieved: 07/01/2025.
- [12] Wallin, Cecilia et al. (31/10/2017). Alzheimer's Disease and Cigarette Smoke Components: Effects of Nicotine, PAHs, and Cd(II), Cr(III), Pb(II), Pb(IV) Ions on Amyloid- β Peptide Aggregation. *Scientific Reports.* 7(1):14423. doi:10.1038/s41598-017-13759-5. Retrieved: 07/01/2025.
- [13] Elbejjani, Martine et al. (2019). Cigarette Smoking and Cerebral Blood Flow in a Cohort of Middle-aged Adults. *Journal of Cerebral Blood Flow & Metabolism.* 39(7):1247-1257. doi:10.1177/0271678X18754973. Retrieved: 07/01/2025.
- [14] Zhong, Guochao et al. (12/03/2015). Smoking is Associated with an Increased Risk of Dementia: A Meta-analysis of Prospective Cohort Studies with Investigation of Potential Effect Modifiers. *PLoS One.* 10(3):e0118333. doi:10.1371/journal.pone.0118333. Retrieved: 07/01/2025.
- [15] Rajczyk, Jenna I. et al. (2023). Relation Between Smoking Status and Subjective Cognitive Decline in Middle Age and Older Adults: A Cross-Sectional Analysis of 2019 Behavioral Risk Factor Surveillance System Data. *Journal of Alzheimer's Disease.* 91(1):215-223. doi:10.3233/JAD-220501. Retrieved: 07/01/2025.
- [16] Hahad, Omar et al. (2021). Smoking and Neuropsychiatric Disease-Associations and Underlying Mechanisms. *International Journal of Molecular Sciences.* 22(14):7272. doi:10.3390/ijms22147272. Retrieved: 07/01/2025.
- [17] Weng, Pei-Hsuan et al. (02/06/2016). CHRNA7 Polymorphisms and Dementia Risk: Interactions with Apolipoprotein $\epsilon 4$ and Cigarette Smoking. *Scientific Reports.* 6:27231. <https://doi.org/10.1038/srep27231>. Retrieved: 07/01/2025.
- [18] Johnson, Adrienne L. et al. (01/01/2021). Cigarette Smoking Status, Cigarette Exposure, and Duration of Abstinence Predicting Incident Dementia and Death: A Multistate Model Approach. *Journal of Alzheimers Disease.* 80(3):1013-1023. doi:10.3233/JAD-201332. Retrieved: 07/01/2025

Contributors Pages

IYNA EDITING TEAM:

Editor-In-Chief: Annie Pan

Managing Editor: Ashvin Kumar

Head of Outreach: Aleksandra Dubno

Head of Assembly: Riyaa Sri Ramanathan

Head of Events: Ananya Karthikeyan

Artist-in-Residence: Kavya Chintakayala

Senior Editors: Divyash Shah, Sai Snigdha Kodali, Vaishnavi Kode, Eesha Oza, Ishani Ghosh, Irene Zhang

Junior Editors: Youlan Li, Mary Zhang, Erin Yoo, Ashley Jing, Gayeong Kim, Xinxin Zhu, Faheem Alam, Abigail Molero, Vibha Yadav Ganji

Head of Journalists: Shrika Vejandla

Journalists: Ambalika Basak, Ellen Seo, Ashra Roshy, Katherine Carpio, Alex Kim

Head of Translation: Ana Beatriz Araujo

Translators: Sebastian Castro, María Fernanda Montiel Quiñones, Brianna Silva, Sofia Fothergill, Purva Sareen, Ipsita Adarsh, Sarthak Kamalkishor Dhole, Namish Balakerthy Punyakoti, GK Tejhaswini, Shokan Zhumadillayev, Sasha Bahdanava, Ayazhan Karimova, Samira Ageyeva

CONTRIBUTING AUTHORS:

Featured Writers: Ashley Keith, Evelyn Gaspich, Mariangel Cisneros

Writers: Joy Kennemer, Beverly Tadeo, Evelyn Gaspich, Mariangel Cisneros, Joy Chastity Spencer-Thomas, Ashley Keith, Samuel Mayers, Jesus Juan, Arian Phillips, Prakhar Singhania

IYNA BOARD OF DIRECTORS:

Chief Executive Officers: Irene Zhang and Eesha Oza

Board Chair: Jacob Umans

ADVISORY BOARD:

Advisory Board Members: Dr. Norbert Myslinski, Dr. Olajide Williams, Dr. Jafri Abdullah,
Dr. Mark Hallett, Elaine Snell

