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The MOST Deadly Disease You've Never Heard of p.8

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Letter from the EIC

Michelle Smith
Editor-in-Chief

Over the past year or so, Grey Matters has come a long way. What began as small academic outreach has grown into a vibrant community that attracts STEM students in Neuroscience, Chemistry, Biology, Psychology, etc. We've become a space where students can channel their scientific curiosity into meaningful, accessible work. I can say with confidence that we are a successful creative outlet for sharing the concepts that have shaped our academic journeys. In doing so, we continue to uphold our mission: to communicate neuroscientific information in a way that resonates with people who aren't well versed in the field.

Our fourth edition has brought a plethora of change, new experiences, and worth ethic. It has been my immense pleasure to serve as Editor in Chief, presiding over a group of outstanding undergraduates with the drive to promote scientific education in any way they possibly can. Many of this semester's contributors have excelled in the quest to spread their knowledge, in the form of poster presentations, k-12 community engagement, and other campus wide initiatives.

I'd like to personally thank my Editorial Board collaborators, in particular Han Kim, for his role in putting the layout together. It looks amazing! I also want to send thanks to Professor David Waxler, our advisor, and Ms. Charlene Martoni, Behavioral Sciences Librarian, for their behind-the-scenes mentorship and guidance. Lastly, GSU's Student Activity Fee Committee and the Neuroscience Institute for their financial support. This exemplifies GSU's willingness to invest in student success – GO Thers'!

It is with great anticipation that the information disseminated throughout this publication will inspire you as it has our undergraduates. Please enjoy!

All the best,

Michelle Smith
B.S. in Neuroscience, Editor-in-Chief

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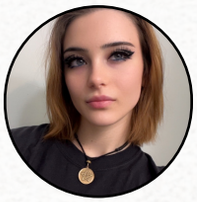

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Prion Disease:

The Most Deadly Disease You've Never Heard of

Author: Lucas Smith
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There is a silent killer out in the world that takes years to present itself. This killer is still at large, causing one of the most fatal diseases known to man, making scientists and physicians question what they know about infectious diseases. This infectious agent is unlike any other. When you think of what causes an infectious disease, most people think of a virus, like the common cold or COVID-19, or bacteria, such as those responsible for tuberculosis. But what if there were another infectious agent with none of these familiar signs, and resistant to sterilization? This mysterious agent continues to challenge scientists' understanding of infectious diseases and neuroscience.

Since the dawn of humanity, mankind has been at war with infectious diseases. Advances in biology and medicine have provided us with more answers than ever before about the causes and treatments of diseases [1]. By the 19th century, scientists had discovered infectious bacteria that could cause disease in humans, leading to the development of methods to sterilize surgical tools. We discovered viruses and created antibiotics to treat bacterial infections in the 20th century. In the 21st century, we can develop a vaccine to end pandemics in a matter of years, as we have with COVID-19 [1].

While our scientific knowledge and treatment of diseases have grown exponentially, many diseases still lack treatment and understanding. There is a rare, unnerving class of diseases with a mysterious cause, strange symptoms, and a 100% fatality rate. Scientists and doctors were unable to identify the pathogen causing these diseases; there was no indication of bacterial or viral infection. It was a scientific and medical anomaly until recently [2].

All these diseases presented with a common symptom of the progressive loss of neurons, known as neurodegeneration, with other symptoms manifesting in a rapid progression. These symptoms include muscle weakness (ataxia), trouble speaking (aphasia), confusion, memory loss, personality changes, and eventually a coma, leading to death in all cases. This group of diseases was determined to be transmissible spongiform encephalopathies, also known as prion disease. Let's break down what that means. Transmissible diseases can be passed from one person to another. Spongiform refers to the large "sponge-like" pore appearance that is formed in the brain through neuronal loss, and encephalopathy describes the observed brain degradation. These rare, deadly diseases challenged our understanding of neuroscience, biology, and infectious diseases as a whole for nearly 200 years. Prion diseases lead doctors and scientists to scratch their heads to this day; even with advances in understanding the mechanisms, the disease still has a 100% fatality rate and no treatment [2]. To understand why, we must dive into the history, mechanisms, and future of these elusive diseases.

"... even with advances in understanding the mechanisms, the disease still has a 100% fatality rate and no treatment."

Prions: Infectious Proteins?

The leading theory on what causes prion diseases has been suggested to be infectious proteins [3,4]. Yes, proteins! You may think of them as nutrients you eat, but in this case, we are discussing the proteins our body produces to function properly. Proteins are composed of amino acids, organic molecules that fold into complex shapes to form the primary structure of proteins. The folding of proteins into complex three-dimensional shapes is necessary for proteins to function properly. Misfolding of proteins can result in a variety of medical conditions, including childhood obesity, blindness, hearing loss, and type 2 diabetes. Without correct folding and functioning proteins, we would be nonexistent [3].

Prion diseases are theorized to originate from misfolded, dysfunctional proteins known as prions, which is short for proteinaceous and infectious virions [5]. The prion protein exists in two forms: a healthy, functional form (PrPC), which plays a role in the creation of new neurons, and the misfolded, dysfunctional form (PrPTSE) that causes prion diseases. How much damage could a misfolded protein possibly cause? Well, researchers would discover that this misfolding completely alters the structure of these proteins, making them resistant to proteases, which our bodies use to break down dysfunctional proteins. This forms amyloid plaques, a buildup of misfolded proteins that can cause damage to our brains. This pathogenic form of the protein can convert other, normal proteins into misfolded forms, creating larger plaques and conferring the infectious characteristics of the protein [4,5].

Evidence suggests that prion diseases can be transmitted in multiple ways, depending on the type of disease [6]. Most forms involve contact or consumption of infected tissue, while some may be genetically transmitted. Prions have been shown to be transmitted through saliva, blood, urine, and milk. Others are transmitted through the contamination of surgical tools, organ transplants, or dura mater grafts in hospital settings. Since prions are resistant to many disinfectants and other sterilization techniques, surgical contamination is a leading cause of infection [6].

Itchy Sheep: Scrapie

The first known cases of prion disease was in 1732, when the English wool industry was disrupted by unfamiliar behavior in their sheep [7]. Sheep were seen scraping their wool off on fences, trees, or rocks as if they had an itch that couldn't be satisfied. These "scraping" sheep then began to show other signs of illness, including weakness in their legs, head tremors, lip smacking, and an unusual posture. This disease was coined "scrapie". Scrapie eventually made the sheep unable to stand and became fatal in all cases. In the 1900s, farmers in the UK began including sheep organs and bones in livestock feed for sheep and cows. Farms benefited economically from this practice, creating cheaper feed. This trend later spread to Europe and the United States. Around this time, there was an increase in scrapie cases, and the disease spread to other countries; however, the cause of the disease remained unknown [7]. In 1938, two scientists named Cuille and Chelle hypothesized that scrapie might be caused by a "slow virus" [4]. A slow virus refers to a virus that remains dormant and takes a prolonged period to manifest, such as HIV. However, this hypothesis would soon be questioned.

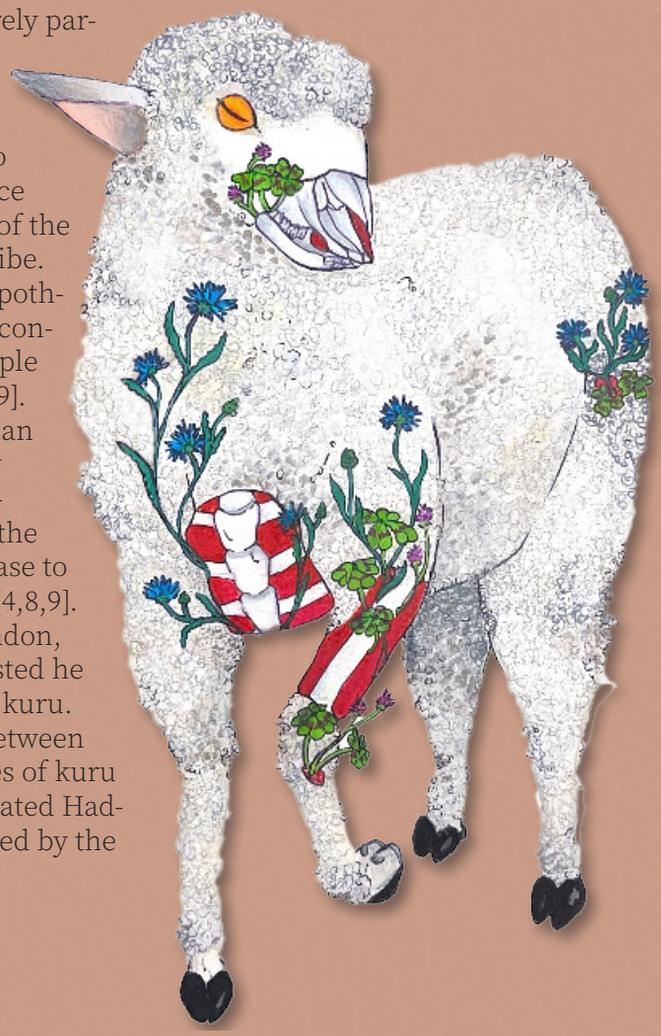
Scrapie exhibited damage in the infected brains with a unique appearance: large pores of neuronal loss were observed in these animals, exhibiting a sponge-like appearance, unlike other known neurodegenerative diseases like Alzheimer's or Parkinson's. In 1944, W.S. Gordon, a veterinarian, attempted to eliminate a virus found in animal brains using formaldehyde, a known disinfectant able to kill viruses. He unknowingly used scrapie-infected tissue and transplanted it into healthy animals. Formaldehyde killed the virus, but the scrapie agent persisted, leading to the death of the treated animals due to scrapie infection. This confirmed that scrapie was indeed

infectious, but resistant to disinfectants, unlike any agent ever seen before [4].

The Tribal Epidemic: Kuru

While discussion of scrapie was still ongoing, a strange degenerative disease of the brain was discovered in the Fore Tribe in a remote region of Papua New Guinea called kuru [4,8,9]. In 1957, scientists Gajdusek and Zigas set out to study kuru. They found symptoms that began with head and joint pain, then muscle weakness, and finally the inability to stand. These symptoms eventually turned into a coma and death. Victims once again exhibited neuronal loss in a spongiform appearance similar to scrapie. This disease was characterized by a long incubation period, sometimes exceeding 50 years [4,8,9].

Kuru was classified as an epidemic in the tribe, killing 1000 people from 1957 to 1961 [4,8,9]. The most favored and earliest explanation of this disease's etiology was that kuru was a genetic disorder, since only members of the isolated tribe were infected. Women and children seemed to be disproportionately affected by kuru, with 60% of cases being women, 38% being children of both sexes, and only about 2% being adult males. However, there was an interesting practice that the Fore Tribe had: a religious practice wherein the dead were consumed by kin. This was not cannibalism, but instead a religious practice done to incorporate the body of the dead into the body of the living relatives. It was found that women and children typically consumed the organs and brain, while men and older boys rarely partook and never consumed the brain or organs. Scientists began to believe this practice may be the cause of the epidemic in the tribe. However, their hypothesis would not be confirmed until a couple of years later [4,8,9]. In 1959, veterinarian William J. Hadlow was studying scrapie in sheep after the spread of the disease to the United States [4,8,9]. While visiting London, a colleague suggested he see the exhibit on kuru. The similarities between microscope images of kuru and scrapie captivated Hadlow; he was shocked by the similarities in the spongiform appearance, neuronal loss, and clinical symptoms presented by both diseases.



After Hadlow's findings, scientists began to believe that kuru, just like scrapie, might be an infectious neurodegenerative disease. This hypothesis was supported by research experiments 4 years later, when the kuru disease was successfully transmitted to lab animals using infected tissue, demonstrating that it was transmissible [4,8,9]. So what happened to kuru? Well, in the 1950s, the Fore tribe's practice was forbidden by the government based on sociocultural reasoning, irrespective of health. Following this, there was a dramatic decline in cases over the next 50 years, until the disease was almost nonexistent. The story of kuru demonstrated that people could contract a disease similar to scrapie found in sheep, and that contact and consumption of infected tissue were capable of spreading these unusual diseases [4,8,9].

Prions in Humans: Creutzfeldt–Jakob Disease

At the same time that scrapie and kuru were being investigated, another strange neurodegenerative disease in humans was being studied by two scientists, Creutzfeldt and Jakob [4,9]. They noted the manifestations of symptoms such as dementia, speech problems, muscle weakness, neurodegeneration in a spongiform pattern, and yet again, a 100% fatality rate. This disease was aptly named Creutzfeldt-Jakob disease (CJD), which would become the most prevalent variant of these prion diseases in humans [4,9]. From 1920 to 1979, there were 1400 reported cases of CJD, all with a similar outcome of progressive dementia, muscle weakness, coma, and eventually death [4,9]. The average age at which symptoms began was 50-58 years. After symptoms began, they rapidly worsened until death, usually 6 to 12 months after symptoms first presented. It was discovered that 50 of the 1400 cases came from families in which the disease affected more than one member. Once again, leading scientists believed that it may be genetic [4,9].

It was discovered that there were two forms of this disease: familial CJD and sporadic CJD [4,9]. Both variants appeared to share the same mysterious mechanisms underlying the disease. It was discovered that a mutation existed in a gene PrP. These gene mutations created misfolded prion proteins, transforming once-healthy prion proteins into unhealthy, dysfunctional ones. Scientists in 1967 suggested that scrapie could be a protein-based disease. However, this hypothesis would be ignored because it contradicted the foundations of molecular biology and infectious disease. By the 1980s, during the "prion era", these prion proteins were finally taken seriously as the leading culprit of these prion diseases and would soon gain global attention [4,9].

Animal Prion Diseases

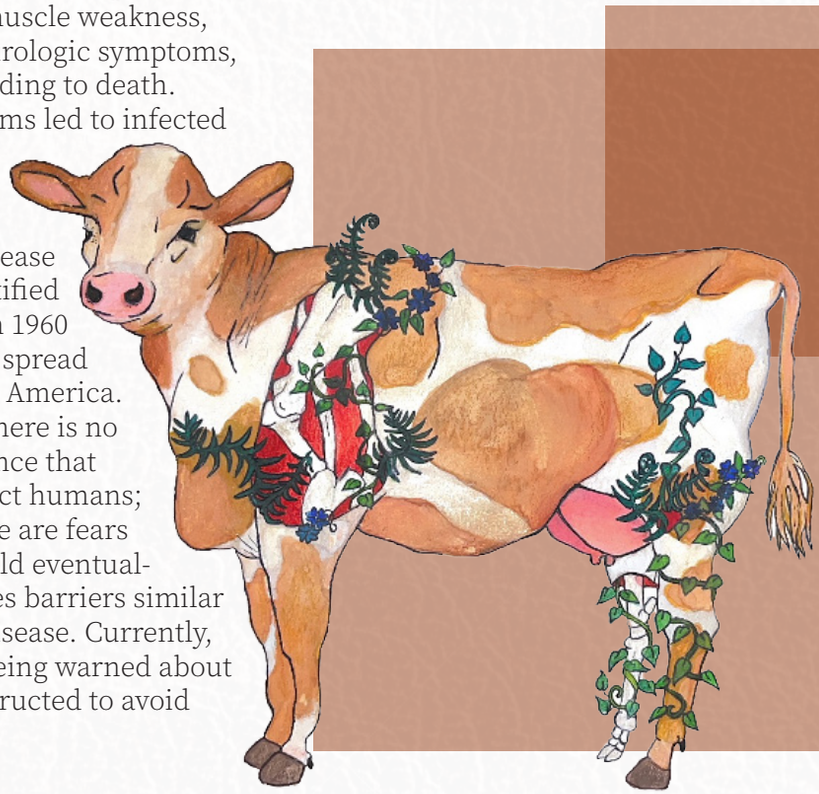
Prion diseases came to public attention during the mad cow disease epidemic, which peaked in the UK in 1992 [10]. Bovine spongiform encephalopathy (BSE), known by the public as "Mad Cow" disease, was another strange neurodegenerative disease, this time present in cattle. Over 2 million cases have been reported to date, spreading across 25 different countries. The clinical signs were similar to those of other prion diseases, including muscle weakness, aggression, and spongiform neurodegeneration in cattle. The most popular theory of the cause of mad cow disease is that the rendering and consumption of sheep carcasses infected with scrapie transmitted prions to cattle. It would later be accepted that consumption of infected tissue, especially brains or spinal cords high in prions, was transmitting these diseases [10].

Mad cow disease caught media attention because it was the first known case of a natural zoonotic prion disease, a disease that can spread between animals and humans [11]. A strange uptick in neurodegenerative diseases set off alarms just after the peak of the epidemic in cattle, and it was believed that mad cow disease was causing a new variant of CJD in humans, known as variant CJD. Physicians and scientists initially didn't understand what was transpiring, but in 1995, when young patients began showing signs similar to CJD, they knew something strange was happening. In the past, CJD was not observed to present itself until around age 50, but this variant strain presented itself differently, specifically appearing in younger ages. The first symptoms were psychiatric, with patients exhibiting anxiety, depression, paranoia, and eventually progressing to muscle weakness and dementia. It was theorized that cooking beef was not enough to kill off infectious prions, the same way cooking beef kills off infectious bacteria. While media coverage of mad cow disease terrified the public, the epidemic quickly became controlled as UK authorities banned the use of meat and bone meal feed for cattle. Cases in cattle dropped 80% the following year, and new cases of variant CJD vanished with it. While only affecting around 200 people, mad cow disease brought prion diseases to the public eye, leaving people terrified to eat beef that may be infected. Government and public health agencies began issuing warnings and setting rules for farms, including requirements for cattle inspections [11].

In recent years, a new animal prion disease has been observed to be spreading in deer, elk, and moose called chronic wasting disease (CWD) [6]. Deer infected with CWD have progressive weight loss, muscle weakness, and other neurologic symptoms, eventually leading to death. These symptoms led to infected deer being referred to as "zombie deer." This disease was first identified in Colorado in 1960 and has since spread all over North America. Fortunately, there is no current evidence that CWD can infect humans; however, there are fears that CWD could eventually cross species barriers similar to mad cow disease. Currently, hunters are being warned about CWD and instructed to avoid consuming deer that exhibit signs of infection; however, research is still ongoing to understand the extent of CWD and the populations affected by it [6].

The Controversy Around Prions

While many of the prion diseases discussed thus far are well-researched, controversy still surrounds prions, which is why it took so long to identify prions as a possible culprit of these diseases, and why some scientists still question this explanation [3,4,6]. To put this controversy into



perspective, the Central Dogma of Biology (CDB) must be understood. The CDB underlies almost all of modern molecular biology. It states that the flow of genetic material is unidirectional, starting with DNA, then to RNA, then to protein. Thus, according to the CDB, proteins cannot be made or multiply without our cells using genetic material to create them. For instance, other infectious agents, such as viruses, follow this theory because they hijack our genetic material to replicate. This underlying theory is what makes prions such a hotly debated issue.

The pathogenesis of dysfunctional prions remains unclear, particularly how it causes the neuronal damage associated with prion diseases. Possible ideas include the loss of the normal functioning prion protein, which may help prevent cell death, or the pathogenic protein itself being neurotoxic. Neurodegeneration seen in prion diseases may also result from an immune response to prions in the brain, where inflammation by our neuroimmune cells (astrocytes and microglia) can cause tissue damage. While it is widely acknowledged that prion diseases are transmissible through contact with and consumption of infected tissue, whether the infectious agent responsible is prions or some other agent causing these proteins to dysfunction remains a topic of hot debate [3,4,6].

Frontiers

So, what can we do about these elusive diseases? Are there treatments? Prion diseases currently have no approved therapies, and to date, there has been no recorded case of a patient surviving a prion disease [15,16]. Most treatments in trials focus on preventing these diseases by specifically slowing the presentation of the dysfunctional prion protein. Scientist Sonia Vallabh has dedicated her life to this research. For her, this disease is personal – in 2010, Vallabh watched her 52-year-old mother die of a rapid, mysterious dementia. Vallabh later learned her mother had passed from the genetic familial form of CJD. She underwent genetic testing and learned she inherited the gene for this genetic prion disease as well, meaning there was a high risk of her developing the same deadly disease later in life. Vallabh and her husband, Eric Minikel, quit their jobs as lawyers and returned to school to study Biomedical Sciences at Harvard. They devoted their lives to discovering a preventative treatment to stop the disease before symptoms manifest. Currently, their lab is focusing on decreasing the number of healthy prion proteins before they get infected, taking fuel away from the ever-encroaching fire.

Vallabh and other scientists have been encouraging individuals with a family history of familial CJD to undergo genetic testing, so they can determine if they have a predisposition to developing CJD. With recent advances in in vitro fertilization (IVF), the familial version of CJD has been successfully genetically removed in humans, meaning children of parents with the familial CJD gene can now be safe from the devastating effects of the gene. Harnessing the power of gene editing has shown to be life-changing for preventing genetic disease with simple mutations like familial CJD, allowing Vallabh herself to protect her children from ever being affected by this devastating disease [15,16].

What Can We Learn

Prion diseases give us a new perspective on our preconceived notions of infectious diseases, biology, and neuroscience [4,9]. Prions have a long and remarkable history, but even 60 years after scrapie was first theorized to be a protein-only disease, our

understanding of these enigmatic neurodegenerative diseases remains limited. The history and the discovery of prion diseases exemplify the point that studying infectious diseases isn't as simple as dealing with only viruses and bacteria. Transmission of disease can exhibit unusual patterns, and identifying these patterns across different diseases will lead to more insights and effective treatments. Discourse on the cause and implications of these prion diseases is still ongoing between scientists, but what we do know is that prion diseases are involved in some of the most fatal infectious diseases known to mankind. These diseases have long incubation periods ranging from a few years to half a century. When symptoms do arise, they progress rapidly and can significantly impact the lives of those affected and their loved ones [4,9].

For now, prion diseases remain extremely fatal, while still infrequent in humans, with only around 1338 cases a year worldwide [15,16,17]. Many dedicated researchers and laboratories continue to study prion diseases, aiming to gain a deeper understanding of the mechanisms and potential treatments for those affected by these devastating diseases. If there's one thing to take away from the study of prion diseases, it's that the brain and the diseases associated with it are complex and multifaceted, but dedicated scientists and physicians work tirelessly to protect you and your family. By looking into the past and future, we can find answers to prevent the spread of disease and save lives. Also, maybe don't eat any brains [15,16,17].

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Neuroscience of Different Attachment Bonding Styles in Infants

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Science Editor: Niyayesh Mollaabbasi
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Artist: Brianna Ellis

A baby tightly clings to their mother's chest as lightning strikes. A toddler plays cheerfully at the playground, knowing their mother is nearby. These mundane moments reveal the brain's natural drive for bonding. Bonding is something that humans are wired to do. Across human evolution, attachment bonding has paved the way for a positive emotional foundation, specifically in infants.

The HPA axis (Hypothalamic-Pituitary-Adrenal axis) is a brain system that controls stress reactions and regulates cortisol, a major stress hormone. Bonding with a caregiver directly reduces an infant's cortisol levels. This stress regulation shapes how babies form attachment. [1] Infants often cry when their mother leaves the room because they have not yet developed a sense of security. When a mother offers different bonding cues such as eye contact and skin-to-skin touch, the infant develops a secure attachment style that helps regulate their stress response [1]. This early regulation lays the foundation for emotional control throughout life.

Early development

When babies feel safe, they are more likely to explore their environment, trusting that their mother is a reliable safety net. Consistent affection and responsiveness helps to build healthy relationships and nurture the brain's emotional development. However, what happens when that foundation isn't established? [2] In a study regarding emotional dependence, infants with insecure attachment were found in a state of extreme distress when their mothers left the room. They displayed distressed behaviours, such as continuous crying. Even when their mothers returned, these infants continued to show deep emotional distress [2]. These behaviors are an indication of long-term problems such as anxiety, social withdrawal, and inability to form healthy relationships

Hormones in Early Bonding

The bonding process profoundly affects not only the infant but also the mother. A key component of this mutual influence is oxytocin, a hormone prominent in attachment and reproductive health. It also increases social sensitivity, which refers to the ability to see and understand how others are feeling based on their cues. [3] Mothers with higher oxytocin levels are not only more likely to engage in frequent physical contact, but this also triggers the infant to release oxytocin. This creates a positive feedback loop. The mother's touch encourages the infant to seek more contact which in turn strengthens the mother's bonding instincts. [3]This cycle is beautifully exemplified during breastfeeding.

There is an essential reason newborns are placed on their mother's chest immediately after birth. This practice is performed for all infants but is especially crucial for babies that were born prior to their due date. [4] This procedure, first observed in South America in the 1970s, began when two physicians faced a shortage of incubators for premature babies and decided to place the infants directly on their mothers' chests. This practice, now standard, helps newborns by adapting to a new environment, and skin-to-skin contact specifically helps regulate the baby's heartbeat, body temperature, and the amount of oxygen in the blood [4].

A study from Stanford University found a strong correlation between skin-to-skin contact and improved neurodevelopmental outcomes, such as improved neural development and coordination. [5] Researchers used a scoring scale to measure development in infants born, on average, 12 weeks before their due date. In the study, seven percent of families did not engage in any skin-to–skin contact, while eight percent did more than 50 minutes per day. An average of 20 minutes of skin-to-skin contact per day was associated with a 10-point increase on the developmental scoring scale [5]. These benefits come from biological changes, like the release of a key hormone known as oxytocin.

The hormone oxytocin plays a vital role in attachment bonding, particularly in skin-to-skin contact. It calms the baby's stress response which reduces anxiety. [6] The gentle contact induced by skin to skin is detected by sensory nerves in the skin known as C-tactile afferents [6]. These nerves signal a brain area known as the hypothalamus which senses internal needs, like hunger and affective touch. Then the release of oxytocin is stimulated which aids in the neurodevelopment of the infant

The practice of skin-to-skin contact has proven to be an influential process that not only brings comfort, but significantly improves the mental and physical well-being of the infant. It stabilizes the infant and provides space for intimate bonding, laying a foundation for healthy connection.

Beyond physical touch, eye contact serves as a primary channel for fostering deep connection. Eye contact between a mother and newborn sparks interesting effects. One of these phenomenons is aligned brain activity. [7] A study conducted at the University of Cambridge measured an adult singing nursery rhymes while looking directly at an infant vs. looking away. Research showed that while the infant and adult held mutual eye contact, their brain activity aligned [7]. This refers to the process of the brainwave patterns of a mother and her baby mirroring each other during close interaction. This alignment fosters a consistent flow of non-verbal communica-

tion and shared positive emotional states.

It has been strongly suggested that newborns have a preference for faces with open eyes. For a newborn, open eyes signal protection. A face with closed eyes resembles unresponsiveness. The game of peek-a-boo provides a sense of relief for the infant when the mother's attentive gaze is shown after a short period of vanishing. While newborns are born with a somewhat clear image of the human face, they are yet to fully develop their ability to see color.

A common misconception is that infants can only see in black and white. They can detect color but it needs to be bold enough for their eye to detect. [8] In a study regarding infant color vision - 75% of infants were able to detect red on a grey background while 80% of infants failed to detect blue. This is likely due to their cones, which allow for color perception, not being fully developed [8]. This preference for saturated colors, more specifically warmer tones, has a direct relation to early social interaction. This means that bright colors aren't just aesthetically pleasing- they're more visually stimulating, making them a powerful tool for facilitating connection.

Massage and Effects on Infants

Massages have different depths and rhythms which can help stimulate the vagus nerve. [10] The vagus nerve is a part of the autonomic nervous system and regulates involuntary functions such as digestion and breathing. To aid in digestion, massages increase the production of digestive enzymes. Stimulating the vagus nerve can also lead to a decrease in heart rate and deeper breathing patterns. This is why the massage can be calming for an infant. Massages can also improve sensory processing, which leads to increased motor development [10]. Sensory processing is the way the infant interprets its surroundings and motor development is their ability to move their muscles.

Infant massages also have a significant impact on the mother as well. [11] Studies have shown that mothers who engaged in infant massages showed signs of reduced anxiety and stronger attachment [11]. During these massages, oxytocin is released due to the physical contact which contributes to the reduced anxiety in mothers. This tactic not only protects mothers from postpartum mood disorders, which refers to the time period after a woman gives birth, but also fosters secure attachment through gentle touch.

These simple nurturing acts- from skin-to-skin contact and mutual gaze to gentle massage- are far more than routine care. They are the fundamental building blocks of secure attachment, weaving a profound connection that lays the foundation for a child's life-long well-being.

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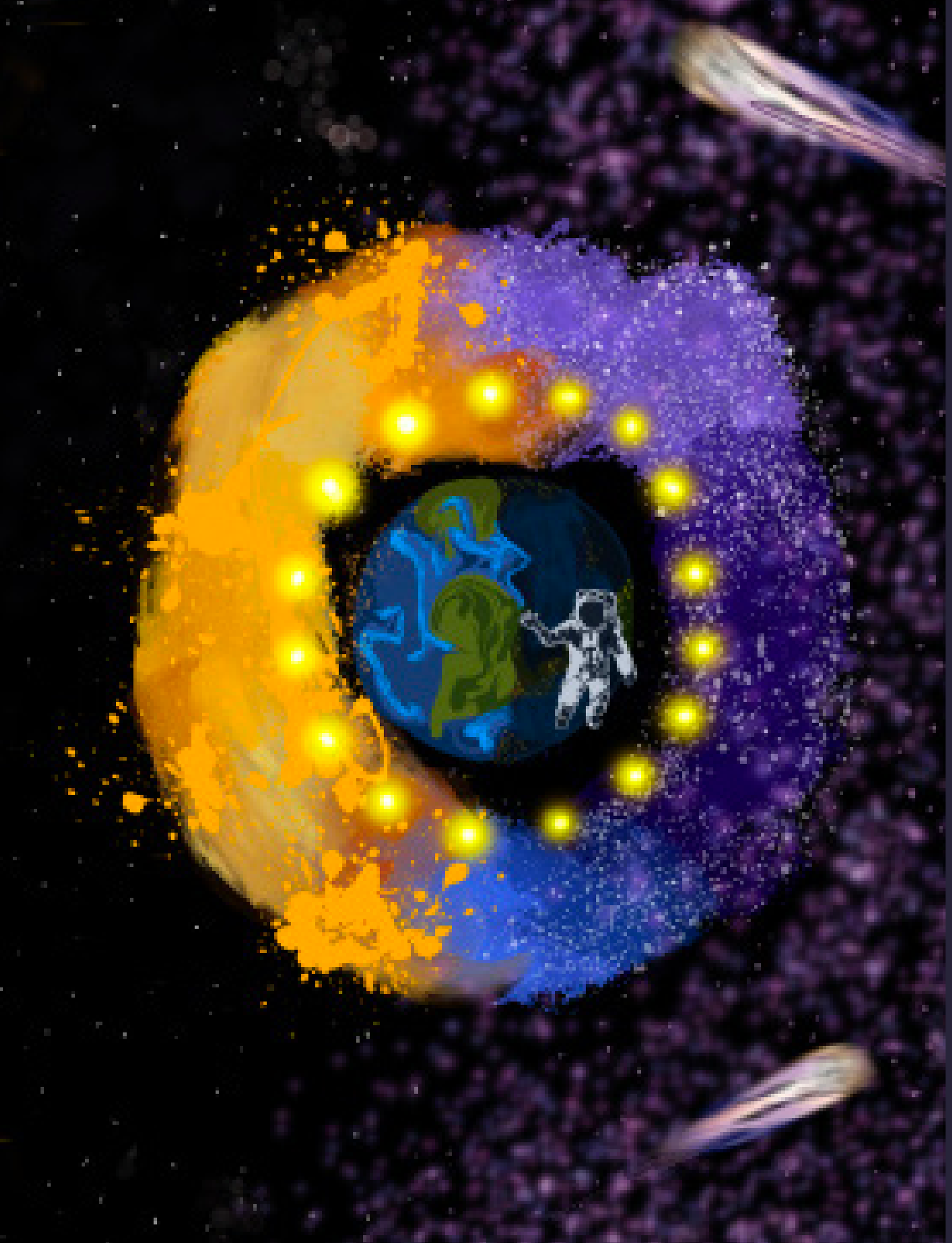

Beyond Earth's Domain

How Space Influences the Brain & Sleep

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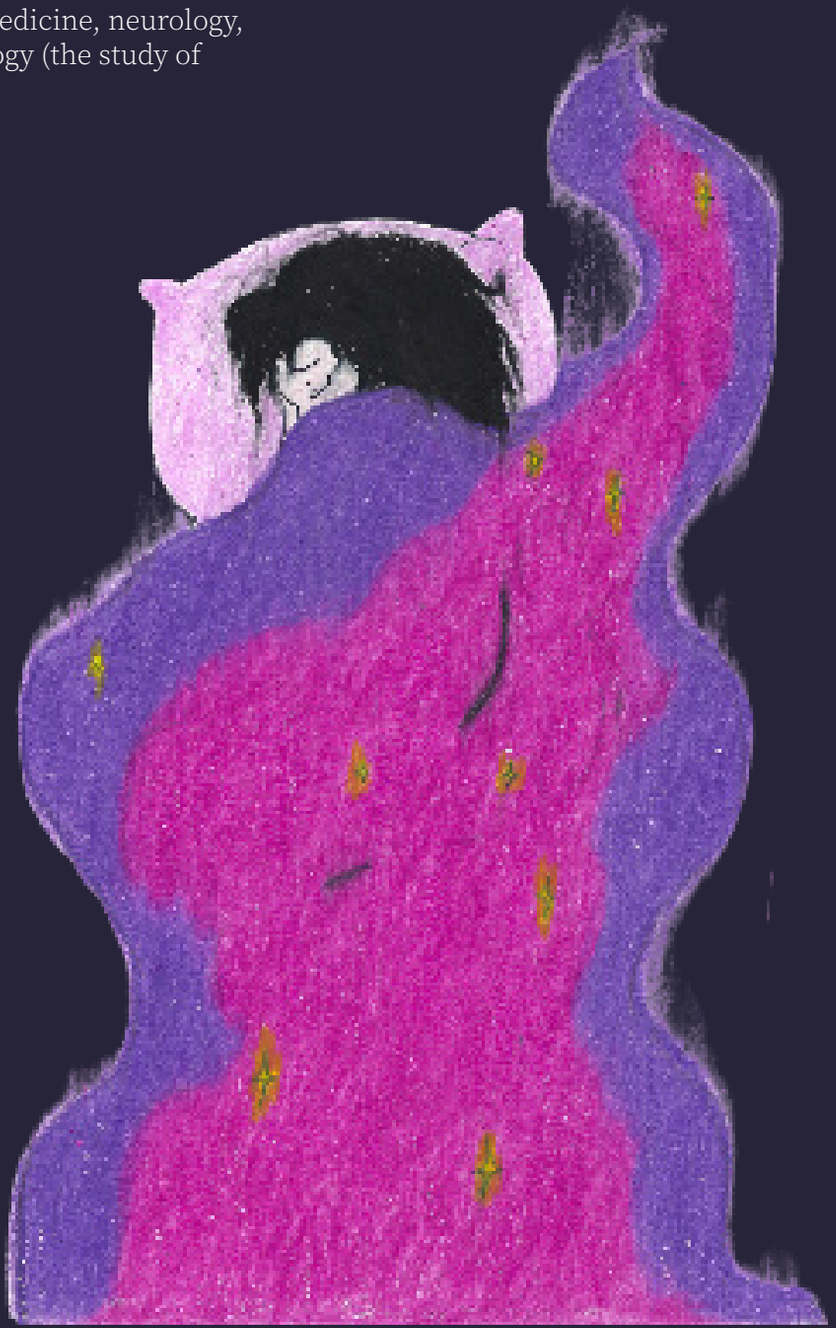
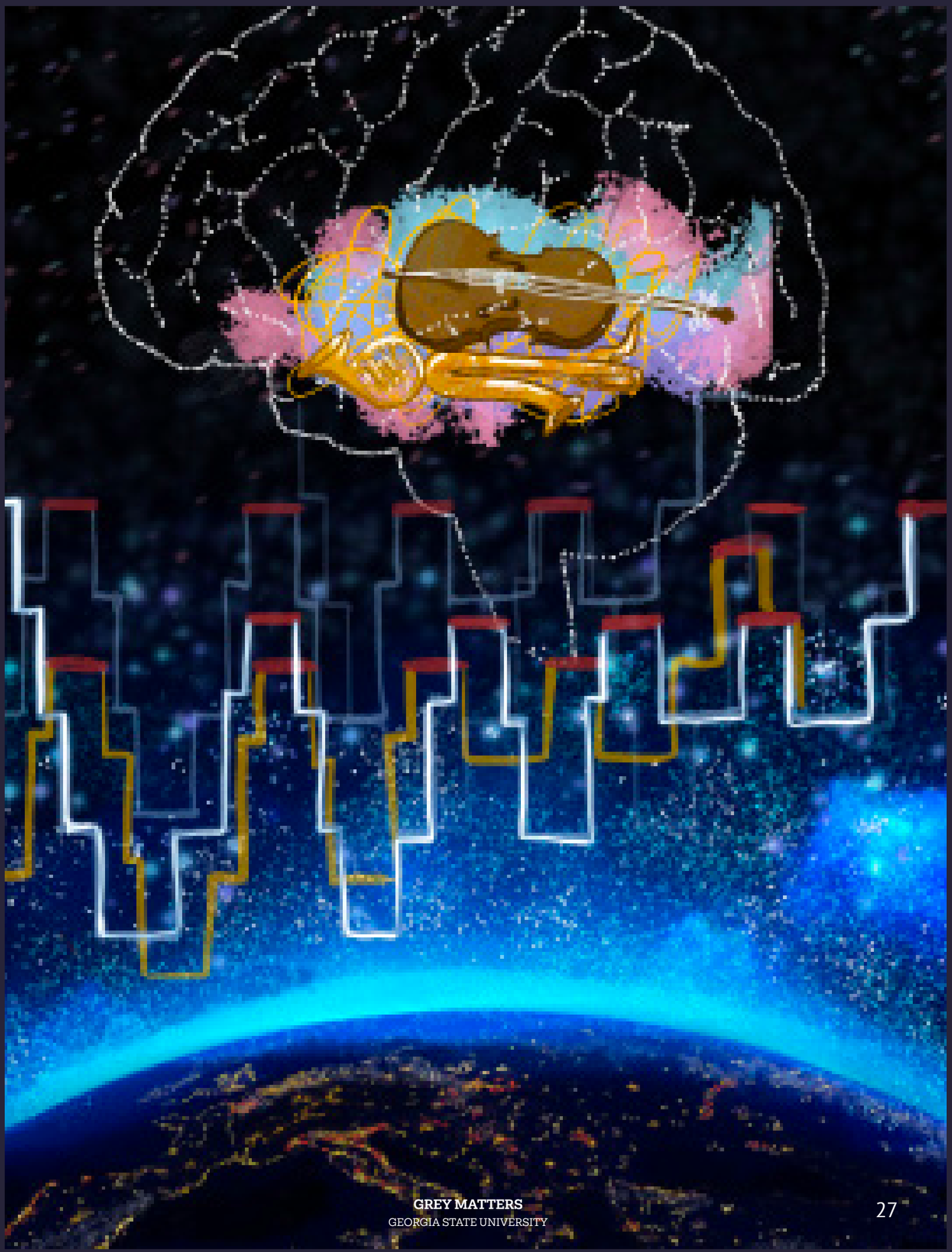
Environments influence the development of organisms, serving as fundamental spaces for growth and evolution that shape how we live and think. Ranging from bubbling oceans to peaking mountains, Earth provides a plethora of homes that are molded for life as we know it. However, outside of Earth's domain, the environment of space is unlike any other humans have experienced; it is an atmosphere of vast exploration. In space, many unfamiliar forces are at play – some we sometimes forget naturally exist. Space provides numerous exposures that challenge human biology as man knows it, including cosmic radiation, microgravity, and disruptions to circadian rhythms [1]. Astronauts traveling far beyond our Earthly domain face these exposures daily, changing routines that we take for granted on Earth. Among these impacted factors, changes to sleep cycles remain one of the most significant effects of space [1].

Understanding the Complexity of Sleep

Often, sleep is misunderstood as a simple process where rest is apparent – a moment where an organism can relax. However, sleep is not that simple; it is rather a series of events composed of physiological and neural occurrences. During sleep, memories are consolidated, emotions are balanced, and vivid dreams are vibrant [2]. Rapid Eye Movement (REM) sleep is characterized by rapid eye movements, accompanied by vivid dreams, a typical loss of muscle tone, and changes in brain activity [2]. REM sleep is crucial for regulating emotions, enhancing cognitive flexibility, and facilitating memory storage [3]. Non-REM sleep is composed of three stages: N1, N2, and N3 [4]. N1 and N2 are considered light sleep, and are when the brain starts to slow as the body becomes accustomed to rest; N3 is when deep sleep occurs and the brain's activity decreases – this stage is also known as slow-wave sleep (SWS) [4]. By understanding how space exposure influences the brain and REM/non-REM sleep, these insights can be applied to future explorations beyond Earth's frontiers and different specialities of medicine and research, such as aerospace medicine, neurology, and somnology (the study of sleep).





Sleep Stages: An Orchestra of Neural Events

During sleep stages, an orchestra of neural events occurs in the brain. For instance, REM increases the activation of the thalamus and limbic system (composed of the amygdala and hippocampus) [5]. These brain regions work together like an orchestra and are crucial for the vividness of dreams, as they enhance emotional processing and utilize sensory signals [5]. During REM sleep, activity is heightened in the thalamus, which modulates cortical sensory regions in the brain. This causes the vivid imagery present in the dreams we experience while sleeping [6]. On the other hand, the amygdala and hippocampus, which are components of the limbic system, are responsible for emotional regulation and memory consolidation [7]. During these stages, the brain and body enter transitions between light and deep sleep as well as dreaming [7]. For Earth-bound individuals, this typically appears as consistent hours of sleep that occur for long durations.

In space, however, astronauts have fragmented cycles of sleep occurring at shorter durations. Research has shown that astronauts spend 26.6% less time in their beds during REM sleep and 9.9% less in non-REM sleep compared to their pre-flight REM and non-REM measures [8]. This significant decrease in REM and non-REM sleep can lead to disruptions in the brain that impact emotional regulation and memory processing. Fragmented sleep cycles can cause the brain to have less time to consolidate memories and regulate emotions. If this becomes a frequent pattern, over time, these disruptions can affect the overall well-being of astronauts and their cognitive abilities [8]

"When the force of gravity is exerted on the human body, it influences the body by affecting the distribution of fluids in the brain..."

Unique Factors: Gravity, Microgravity, & Cosmic Radiation

Many external factors influence the quality of sleep in space. On Earth, there is a force called gravity that influences our body's posture. Gravity produces an external force on one's body, affecting the body's posture in a given area [9]. On Earth, when the force of gravity is exerted on the human body, it influences the body by affecting the distribution of fluids in the brain [10] and maintaining a body posture that does not resist the gravitational effect [11].

However, in space, astronauts experience a state of continuous free-fall, causing microgravity; microgravity is an apparent state of weightlessness [11]. This reduction of gravity can create resistance on bodily posture when sleeping, resulting in the need for external forces to maintain one's posture. This can cause sleep disturbances to occur at a higher rate in space due to changes in gravitational strength [11]. As a result, space environments can cause a reduction in sleep duration, with decreased periods of deep sleep due to microgravity [12]. Despite this, countermeasures have been adopted to minimize these effects;

pharmacological interventions, such as the use of medications like modafinil (which promotes wakefulness), have been noted as stimulants used by astronauts during their missions – highlighting how the application of sleep medication is not confined to Earth [12]. Further studies could shed light on the physiological and sleep implications of pharmacological interventions on astronauts during long-term missions.

Cosmic radiation also presents an interesting element in space. Cosmic radiation is the sum of charged, high-energy particles [13]. In rodent models, exposure to cosmic radiation has been shown to result in a decrease in performance in the hippocampus – a brain region vital for learning and memory [14]. It was also noted that the mice experienced increased neuroinflammation and decreased cognitive behaviors [14]. These space effects can also increase the development of cancer and neurodegenerative deficits in astronauts [15]. This research highlights that cosmic radiation can threaten the neural circuitry of exposed organisms, underscoring the importance of space research in protecting the brain and body health of astronauts [15].

"...exposure to cosmic radiation has been shown to result in a decrease in performance in the hippocampus – a brain region vital for learning and memory."

A Change in Circadian Rhythm: Disrupted Body Clocks

On Earth, a 24-hour cycle is followed to transition between day and night [4]. Naturally, the body undergoes this transition to create a body clock that is accustomed to waking at certain hours of the day and resting at other times. This is known as the circadian rhythm, a biological cycle that follows a 24-hour timing system [4]. The circadian rhythm is controlled primarily by the suprachiasmatic nucleus (SCN) of the hypothalamus [16]. The SCN sets the pace for the body's daily routines in many ways. For instance, the SCN sends signals to different regions of the brain to help control sleep via light signals received from the eyes. These signals help the SCN regulate the secretion of melatonin, a hormone released in response to light levels. Changes in light exposure, temperature, and overall sleep routine can impact the release of melatonin, leading to disruptions in sleep cycles [16]. Light exposure is significantly increased in space, as the International Space Station orbits the Earth every 90 minutes – causing 16 sunrises and sunsets for the astronauts [17]! Exposure to frequent sunsets and sunrises can therefore disrupt the astronauts' internal clocks, which reduces overall sleep. Protocols have been introduced to help astronauts maintain circadian rhythms and improve sleep [18]. On the NASA International Space Station, LED lights are used to help simulate the Earth's natural light and dark cycles [18]. These protocols are continually improving, providing avenues for adaptation to the various demands of space environments. Ongoing research has focused on the usage of dynamic lighting systems (DLS) to explore ways to prevent fatigue through flexible sleep schedules [19]. DLS focuses on optimizing light cycles between blue-depleted white light to reduce alertness before sleep, blue-enriched white light to increase alertness before sleep, and white light for normal vision [19]. By introducing DLS protocols to astronauts, lighting schedules can better support the physiological differences present in future space missions.

To Infinity & Beyond: Importance of Space Research

Researching how space influences brain function and sleep cycles provides opportunities to improve astronaut health, whilst also understanding the applications of neuroscience beyond Earth. Through understanding how sleep stages, unique factors, and circadian rhythms affect brain health, researchers can learn how physiology and environmental changes function in extreme conditions. This could reshape what is known as the human experience, offering a glimpse of what the future may hold beyond our frontiers.

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Giggles and Gray Matter:

How Laughter Changes the Brain

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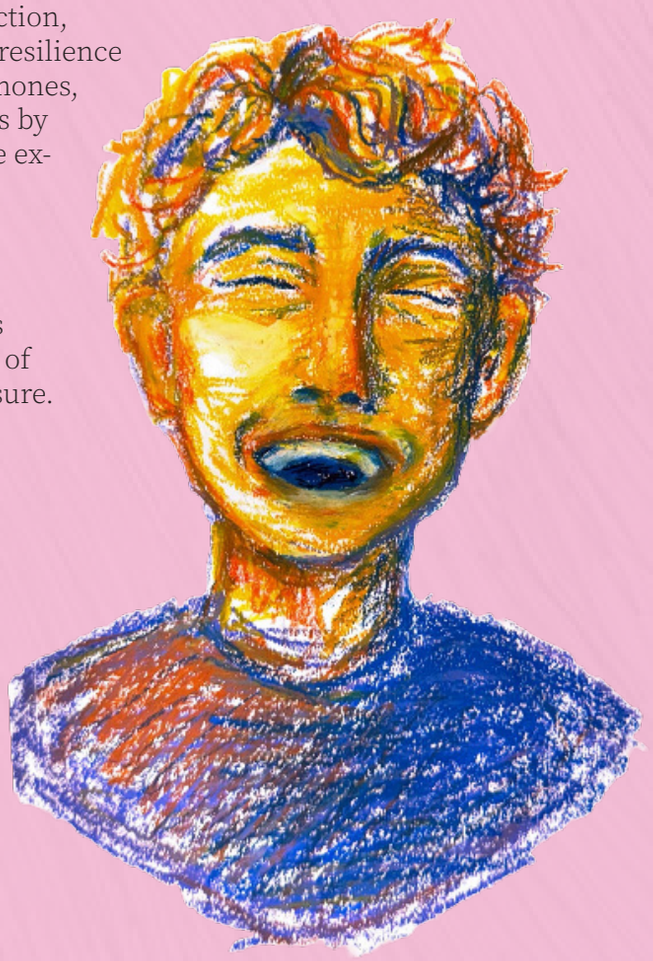
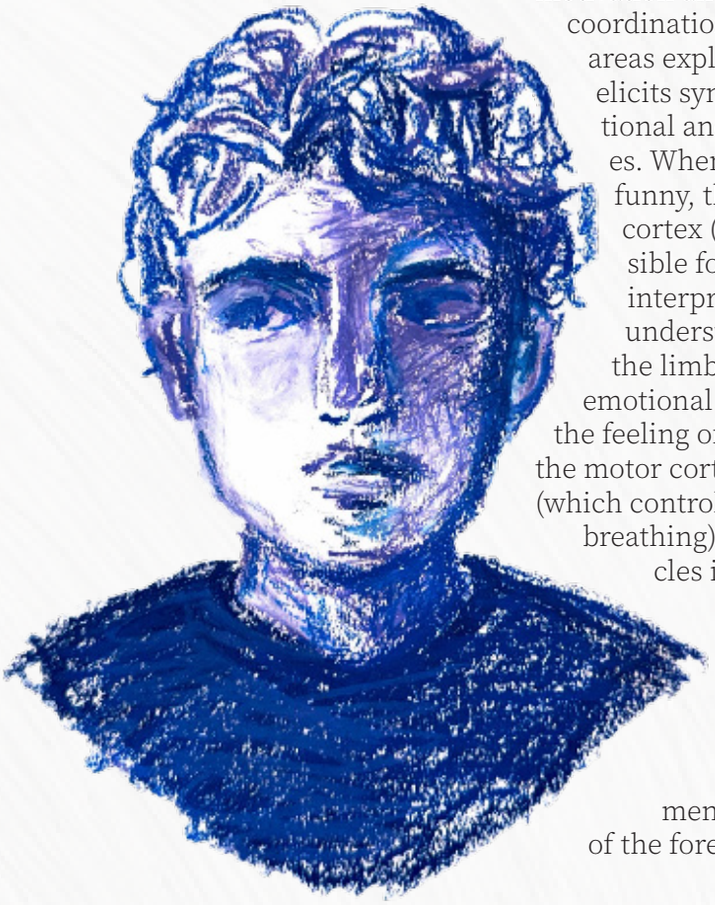
Picture this…You're hunched in your seat in a crowded lecture hall after hours of studying, your notes blurring together and your eyelids dragging with every blink. The room feels heavy and silent until your friend cracks a joke out loud. Suddenly, the quiet breaks. A spark of laughter rises from you, then spreads across the room like a wave, lifting the energy and pulling everyone back to life. The tension in your mind begins to fade, your heart rate slows, and the day feels brighter. In that sudden and simple moment of laughter, your brain goes through a variety of neural and chemical reactions that improve your mood, connect you with those around you, and clear the racing thoughts in your head. While many think that laughter is a reaction to humor, neuroscience has shown that it is one of the brain's most beneficial emotional responses. Laughter enhances cognitive performance by increasing oxygen flow and releasing neurotransmitters that improve brain function, strengthens emotional resilience by reducing stress hormones, and fosters social bonds by creating shared positive experiences that increase trust and connections with others. Laughter is crucial, especially among college students navigating new aspects of life and academic pressure.



Inside The Brain's Response To Humor

Laughter may seem like a simple reflex, but it engages a complex network of brain regions [1]. According to the National Institutes of Health, the prefrontal cortex helps us interpret and recognize humor, while the limbic system, a part of the brain that controls emotion, memory, and motivation, manages emotional reactions



[1]. When we find something funny, signals travel through the amygdala and hypothalamus, areas that regulate emotions and bodily responses, before activating regions in our body that cause us to physically laugh. MRI studies, brain scans that show which areas are active by measuring blood flow, over the past decade have identified activity in the supplementary motor area in the medial frontal cortex, a reward center associated with motivation and pleasure [2]. The coordination of these brain areas explains why laughter elicits synchronized emotional and physical responses. When something seems funny, the prefrontal cortex (the region responsible for reasoning and interpretation) helps you understand the humor, the limbic system (the emotional center) generates the feeling of amusement, and the motor cortex and brainstem (which control movement and breathing) activate the muscles in the face, chest, and abdomen to produce laughter. Simultaneously, the nucleus accumbens and ventral tegmental area—two parts of the forebrain involved in reward—release dopamine, a "feel-good" chemical that lifts mood and makes the experience enjoyable. This dopamine surge provides a natural high for humans, similar to what we experience after a workout or listening to music, suggesting that laughter acts as a built-in mood enhancer [2].

"This dopamine surge provides a natural high for humans... suggesting that laughter acts as a built-in mood enhancer."

Laughter is Therapy

When we laugh, our brains release endorphins, natural chemicals that work like the body's built-in "feel-good" medicine. Endorphins lift your mood and also help reduce pain by interacting with the brain's pain-relief system. A study performed in 2022 by the University of Oxford wanted to understand if there was a correlation between laughter and the release of endorphins, which help people feel good and reduce pain. To test this, participants watched either funny videos, neutral documentaries, or live performances, and their pain tolerances were measured before and after. The researchers found that people who laughed actually had higher pain tolerance because their brains released more endorphins [3]. This means that laughter doesn't just make us feel good, It changes how our body responds to pain by activating the brain receptors affected by painkillers and antidepressants. Laughter also helps to lower cortisol levels, the primary stress hormone in our bodies. High stress levels can be extremely common in college students, especially during exam season. According to researchers at Morinomiya University of Medical Sciences, laughter therapy lowers the hormone adrenaline, which is responsible for increasing heart rate and blood pressure, helping people feel calmer and think more clearly [4]. Joking around with friends, watching a funny video, or recalling something that makes you laugh can help lower stress and put you in a better mindset for learning.

Humor and amusement also boost the brain's efficiency in several surprising ways. Neuroscientists have shown that laughter activates the prefrontal cortex, the part of the brain used for thinking, planning, attention, and decision making [5]. When you comprehend a joke, your brain releases dopamine, a chemical that boosts focus, plea-

sure, and motivation. Dopamine not only makes you feel good, but it also activates the hippocampus, the brain's memory center. When dopamine levels rise, the brain stores information more effectively. In an academic setting, this chemical boost can be extremely helpful [5]. For example, students often remember funny examples or humorous stories from class more easily than dry facts because dopamine strengthens the formation of long-term memories. Humor also reduces mental fatigue by breaking up long periods of focused thinking, giving the brain short resets that improve cognitive flexibility. This makes tough subjects feel more approachable. Adding humor to study sessions, like creating funny acronyms and joking about certain concepts, can make learning more engaging and enjoyable. For college students who face constant academic pressure, incorporating humor into daily studying can transform stressful subjects into something more enjoyable and less intimidating, which will overall improve both performance and confidence.

The Hidden Benefits Behind A Good Laugh

Human connection is also strengthened through shared moments of amusement, making laughter one of the oldest and most natural forms of human bonding [6]. According to the Department of Experimental Psychology at the University of Oxford, laughter originally helped early humans to cooperate, signal safety, and build social alliances. When we laugh with others, our brains mirror each other's emotions using special cells called mirror neurons. These neurons fire both when we laugh and when we observe someone else laughing, which allows us to naturally pick up on their joy and join in. The shared brain activity helps people feel emotionally in sync. Beyond this, laughing together triggers the release of oxytocin, a hormone associated with trust, empathy, and social bonding. Oxytocin strengthens relationships by creating feelings of comfort, belonging, and closeness. For

college students who often face loneliness, social anxiety, and academic pressure, these bonding effects can be especially powerful. A shared laugh can break awkward tension, ease the stress of group projects, and make meeting new people less intimidating. Over time, regular moments of laughter help friendships form more naturally and deepen existing relationships. Humor acts as a social glue, creating an environment where students feel connected, supported, and understood [6]. Laughter also plays a prominent role in improving mental health. Many college students deal with depression and anxiety, which are often linked to imbalances in brain chemicals like serotonin (helps regulate mood), dopamine (the motivation and reward chemical), and Gamma-aminobutyric acid (GABA) (a calming chemical that slows down racing thoughts) [7]. Laughter naturally helps restore balance by activating neurochemical pathways associated with calmness and well-being. According to the National Institutes of Health, laughter increases GABA activity, a brain chemical that promotes calmness and relaxation—similar to what happens during meditation or yoga. Laughter supports brain chemistry naturally; it acts as a free form of therapy. This effect explains why even a quick laugh can instantly make you feel lighter or help break a cycle of stress or overthinking. Laughter also interrupts rumination, when someone gets stuck replaying negative thoughts. When we laugh, the brain shifts into a more present, less stressed state, giving us a mental reset. Over time, these small moments help build emotional strength and make it easier to handle challenges [7]. For college students, nearly half of whom report experiencing depression or anxiety, finding simple, enjoyable coping tools is essential. Laughter-based activities like watching comedy shows and spending time with friends give students a natural low pressure way to improve their mood. These shared moments also create a supportive social environment.

Laughter's Impact On The Mind

From an evolutionary perspective, laughter likely evolved as a tool for emotional regulation and connection long before humans understood it scientifically. According to researchers, most laughter happens during ordinary conversations rather than when someone tells a joke [8]. This shows that laughter is more about bonding, not just humor. Babies start laughing around 3 months old when playing or interacting with parents. These early moments of laughter help to form the brain circuits responsible for connection and emotional control. As we grow, those same brain regions stay active when we laugh, proving that laughter is deeply rooted in human biology. Laughter can also help the brain stay healthy as we age. When you laugh, your breathing deepens and oxygen flow increases, sending blood to the brain. The boost in circulation helps brain cells stay active and releases Brain-Derived Neurotrophic Factor (BDNF), a protein that supports learning, memory, and neuron growth.

"This means laughter-based activities... could help improve campus mental health in a social and enjoyable way."

More BDNF gives the brain a better ability to adapt and learn new things. Psychologists explain that positive emotions like joy and amusement expand how we think and see the world. This makes us more creative and open-minded [9]. For college students facing stress and constant change, laughter keeps the brain flexible, resilient, and motivated.

Overall, laughter is not just about entertainment. It is a significant tool to strengthen yourself mentally. By releasing endorphins and dopamine, laughter lowers stress, improves focus, strengthens memory, and builds social connections. For college students balancing pressure from school and social life, laughter can be one of the simplest and most effective tools for self-care. Taking time to laugh, whether during a study break, while hanging out with a friend, or even watching funny videos on your phone, is not a waste of time. It recharges your brain and helps you connect with others. In short, laughter is nature built into medicine for a healthy, happy, and focused mind.

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Queer Identity and Neuroscience

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Queer identity has historically and currently been under political and social scrutiny. Despite the long-standing presence of queer individuals and the fundamental role of gender and sexuality in human nature, there remains significant controversy surrounding the topic [1,2,3]. In this paper, I will address the history surrounding queer identity and how this influences research today, discuss the ways history has influenced stigma and marginalization, introduce some current research, and discuss future directions for research proposed by scientists [1,2,3].

The LGBTQ+ community includes lesbian, gay, bisexual, transgender, and queer/questioning communities (LGBTQ+). Queer identity will be defined as a sexual orientation or gender identity that falls outside of the cultural norms of heterosexual and cisgender people. Cisgender (cis) is someone who identifies with their gender assigned at birth (i.e. born male and identifies as male) and transgender (trans) refers to someone who does not identify with their gender assigned at birth (i.e. born male and identifies as female). Put simply, queer refers to non-heterosexual and/or non-cisgender people.

Background

A driving misconception often used to drive homophobic and transphobic ideologies is the idea that queerness is a choice triggered by behavior and experience having no biological basis. The problem – all behavior is triggered by experience and biology–this is not exclusive to gender identity or sexual orientation [1]. Understanding sexuality through brain circuitry gives us a deeper understanding into biological evolution, how stigma affects the brain in marginalized communities, and how to "better quantify variation among many brain types." We will further elaborate on the investigation of stigma on the brain and behavioral research in a later section–discussing current studies [1].

In Edmiston and Juster's article "Refining Research and Representation of Sexual and Gender Diversity in Neuroscience," they discuss the history of LGBTQ+ neuroscience research and the intersectionality of its relationship to politics [2]. In addition, they address how there is no way to depoliticize LGBTQ+ research, especially considering the past as some research has contributed to the current cultural prejudice as it relates to the LGBTQ+ community. They claim scientists have a duty to address the harm caused intentionally or not. Investigation of the biological cause for queerness was used to support LGBTQ+ rights and in other ways has been used to perpetuate the idea that there is a "fix" for queerness [2].

The idea that queerness has a specific biological cause is linked to outdated forms of biological determinism and the eugenics movement [2,4]. The eugenics movement was the idea that a society can selectively breed as a means to improve the human race [5]. Eugenicists aim to breed out the "bad traits" of society–traits typically tied to being in a marginalized community like people of color, poor

people, disabled people,etc. Regardless of the intentions of the scientists to support LGBTQ+ rights, without understanding this historical context there is room for the reinforcement of harmful ideas like this [1,2,4,5].

Harmful Rhetoric That Has Influenced Stigma

Over time, through various movements and social change, the way we view gender and sexuality has broadened but there is still much work to be done [1]. There remains a gap in education that contributes to the perpetuation of stigma concerning gender and sexuality. An explanation for such is due to the continued stigma surrounding queer identity–paradoxically–many believe "focus on LGBTQ sexuality would be inherently sexual, salacious and incorrect" [1]. Some of the stigma and harmful stereotypes derive from a fetishizing of the queer identity. These stereotypes have a history in neuropsych research regarding LGBTQ+ identity. In the 1960s–1970s queerness was associated with criminality and psychiatric disorders [2,4]. Even the terms pathologizing LGBTQ+ identity as "sexual deviation" and "sex psychopaths" frame queer identity as predatory [6].

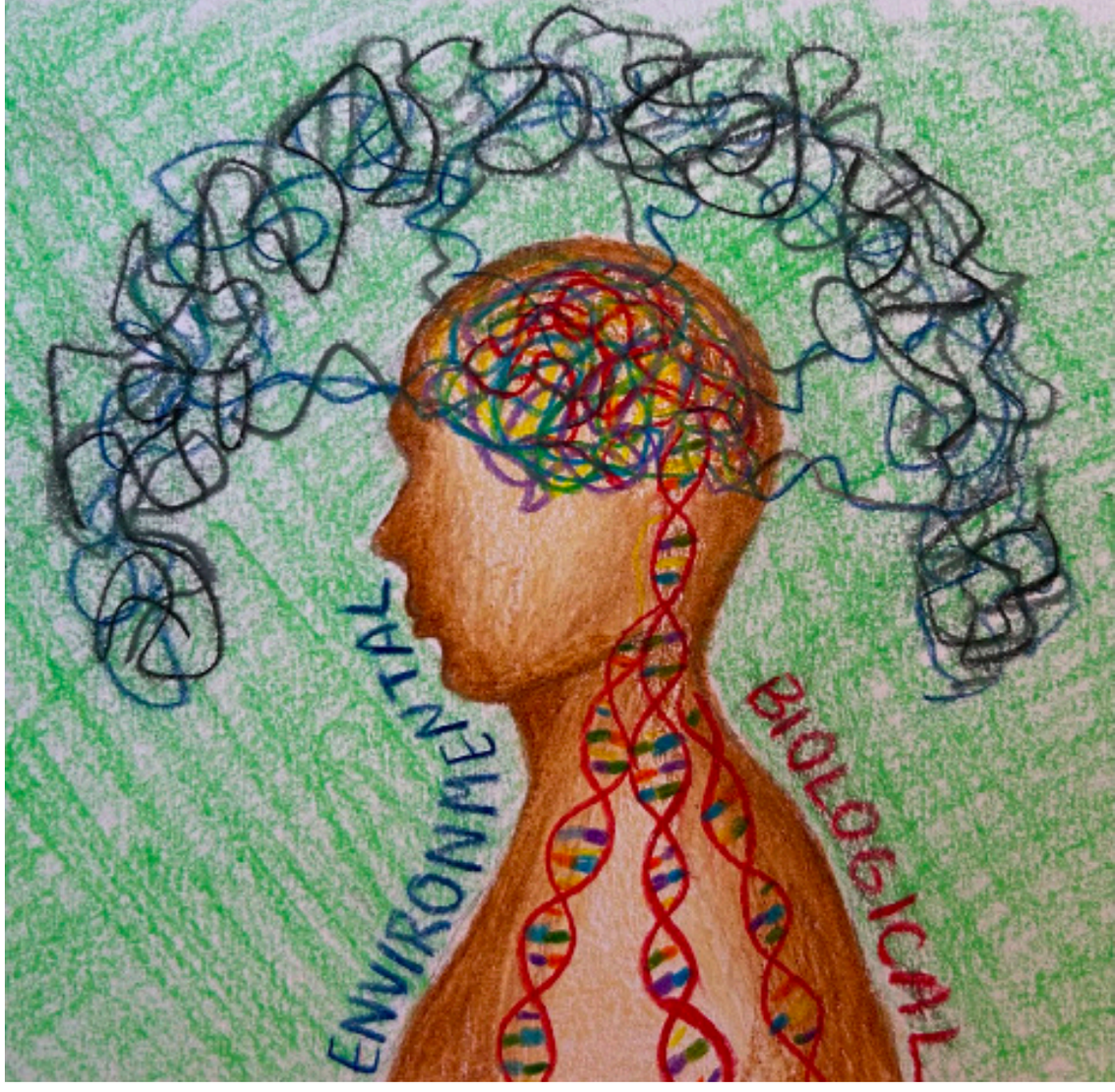
In a neuro journal review by Edmiston and Juster, "Refining Research and Representation of Sexual and Gender Diversity in Neuroscience" they criticize studies that focus on erotic stimuli to validate LGBTQ+ individuals claiming it "suggests an unnecessary preoccupation [2]." Suggesting an overkill of focus on erotic stimuli response when there is more to sexuality than that [2,4,6].

Cultural views have direct impacts on the mental health of LGBTQ+ individuals [1]. In D'Almeida's research journal article, "Neuroscience of Heterosexuality and Homosexuality" they discuss how parental restrictions concerning anti-queer views contribute to children's social attitudes outwardly and within their own identification. Inclusion and education is a mending factor as it relates to discrimination against minorities. Intergroup contact theory states that "personal interactions are a major avenue through which prejudice is reduced." The main cure for stigma is day-to-day interactions and learning how to be culturally aware and culturally sensitive. Exposure to queer identity and educators informed about how to foster an environment of neutrality has proven to help queer youth feel more comfortable with their identity [1].

Neurocognitive Health Research

Neurocognitive health studies give us a better understanding of the progression of cognitive decline in older LGBTQ+ adults. Studies on Alzheimer's disease found that in older genderqueer people, there was a nine-fold

"The main cure for stigma is day-to-day interactions and learning how to be culturally aware and culturally sensitive."



higher risk than older adults in same-sex relationships [3]. As we lean into discussion of the risk of neurodegenerative diseases within the LGBTQ+ population, there is limited research but, "compared with heterosexual and cisgender groups, queer people show higher rates of subjective cognitive decline." (SCD refers to the self-perception of cognitive deterioration as defined earlier within the article.) However, this does not guarantee someone is experiencing symptoms of cognitive decline. A self-perception of cognitive deterioration can be caused by other things and is not a good indicator of risk. While evidence remains inconclusive, heightened exposure to stigma, stress, depression, and suicidality among LGBTQ+ individuals may contribute to increased neurodegenerative risk [3].

Older queer people have faced greater stigmatization with things like "Gender Identity Disorder", "Sexual Deviation" and "Ego-Dystonic Homosexuality" being considered a mental disorder in the DSM (Diagnostic and Statistical Manual of Mental Disorders; used for diagnosing mental disorders) at some point in time [3,4,8]. In addition, older queer people had fewer civil rights in place to protect the LGBTQ+ community, all factors contributing to minority stress [3,8].

Gender-Affirming Care Research

In a neuroscience review article by Melissa E. Wright and Kevin Murphy they discuss research concerning transgender health investigating cerebrovascular (blood vessels in the brain) changes with gender-affirming hormone replacement therapy (gaHRT) [6]. Gender-affirming hormone replacement therapy (gaHRT) is a tool genderqueer people can use as a means to aid in their transition, the two main forms being masculinizing and feminizing. Hormone replacement therapy is a form of gender-affirming care. It is to be noted, gender-affirming care is not specific to the LGBTQ+ community [6].

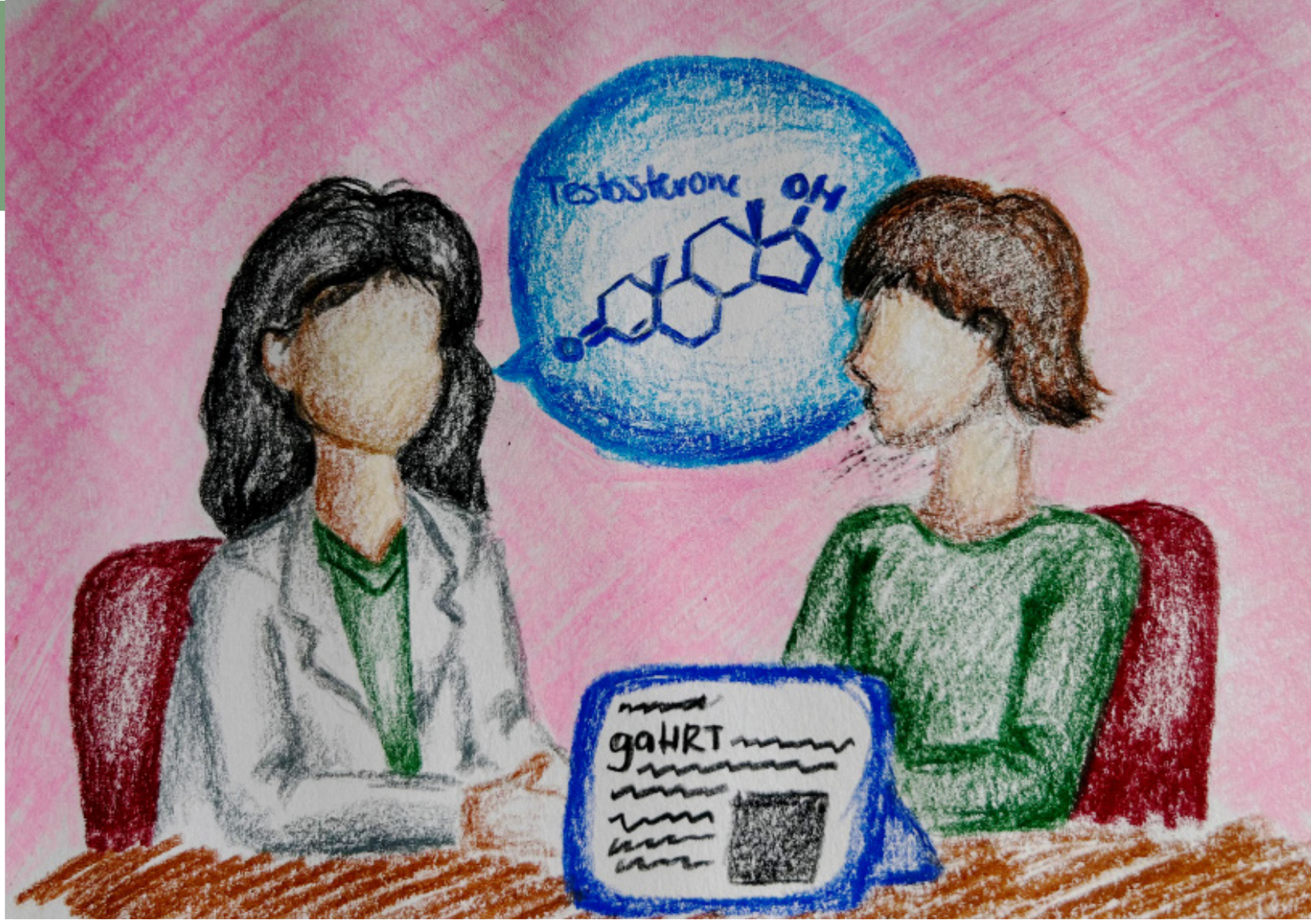
To briefly explain how gaHRT can work, if someone is assigned female at birth and wants to undergo a medical transition to male, they can take testosterone to aid their transition [6]. Gender-affirming care has been shown to improve quality of life for those who undergo this therapy however the day-to-day struggles that queer people face with discrimination and stigma is a problem that continues to negatively affect their health. Research on cerebrovascular impacts from gaHRT is important because hormones have an effect on your brain and your blood is vital for cognitive function. In addition, when it comes to treating transgender patients we must recognize due to their hormonal treatments, they "may present with different healthy reference levels than their cisgender counterparts." Specifically focusing on transgender women, due to vascular changes, they present increased risk for stroke even without long-acting estrogen use. This changes through time, with a need for longitudinal research… "cerebrovascular event risk was unchanged initially and only increased after the 6-year follow-up." In general there is a need for more research to be done concerning gender-affirming hormone replacement therapy to improve on the quality and understanding of health care for those who need gender affirming care [2]. It is important to note due to the increased reports could, "be due to health care barriers and other environmental factors (e.g., minority stress) rather than gaHRT" [6].

I want to reiterate that gaHRT has been proven to improve quality of life overall–from alleviating feelings of depression, stress, gender dysphoria and day-to-day life [6]. Therefore, this information should not deter someone from seeking gaHRT rather to be informed that there is more work to be done overall to improve the way we understand and treat gender-affirming hormone replacement therapy[6].

fMRI Study

When it comes to the investigation of neuroanatomy between hetero and homosexual individuals, ongoing studies provide evidence for slight differences through Functional Magnetic Resonance Imaging (fMRI; shows which areas of your brain are most active) scans [9]. The major takeaway from this study–there is unlikely a singular neuroscientific explanation for sexual orientation because there are other factors involved like cognitive (thinking) and emotional responses to our environment[10,11].

In a study investigating sexual orientation, researchers were looking to see what areas of the brain are active in the resting state and how that relates to sexual orientation by comparing a group of 26 hetero and 26 homosexual men using fMRI [10]. This study was conducted specifically in the resting state because other studies similar to this used erotic stimuli to look at potential brain differences–



which they found to be limiting because the neural reaction to erotic stimuli could have been specific to that task rather than sexual orientation. They found some differences between participants that could potentially help future investigation of sexual orientation but overall needs more research [10].

Problems

A major issue when it comes to the investigation of queer communities is how the sample size is not ethnically diverse– mainly including white people, which is not representative of the LGBTQ+ community [1,2,3]. Concerning cognitive health in queer communities, "when ethnicity data was collected people of color have been systematically underrepresented in most of the studies... and often make up less than 15% of the sample... preventing clinically meaningful analysis and leading researchers to choose race/ethnicity as a covariate". In addition, many LGBTQ+ people do not trust this research out of fear of safety or the belief there will be no benefit to the research–also known as research fatigue, "where members of a small, vulnerable minority communities become exhausted by repeated requests to participate in research with little to no benefit for their community." It can be exhausting to lean on a field that you are not sure that you can trust, considering the dark past and not being sure the research you are contributing to benefits your community or has the potential to contribute to even more harm [1,2,3].

Overall a consistent theme from paper to paper is the

call for a more inclusive sample size, a need for compassion and collaboration when investigating marginalized communities and more research.

Conclusion

This research has potential to further understand sexuality and gender expression on a deeper level in addition to understanding how minority stress can affect the brain over time. Education and inclusion is a driving force as it relates to breaking down the barriers of stigma and prejudice in addition to diversity being a proven way to help the youth feel better about their own identity. Current research about neurocognitive health and gender-affirming hormone replacement therapy could give scientists and doctors more effective ways of treating health conditions solidifying its importance. In addition, to ongoing neuroanatomy research that could further society's understanding of sexual orientation.

"Education and inclusion is a driving force as it relates to breaking down the barriers of stigma and prejudice..."

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