FEATURED ARTICLES

The Blood Brain Barrier: An Overview
- Soleil Ava Wizman

A Multi-Factored Experiment Testing the Effect of Magnitude of Change on Perceptual Ability
- Atul Venkatesh & Jeffrey He

Huntington's Disease: Potential RNA-based Treatments
- Aleksandra Dubno
The Blood-Brain Barrier: An Overview  Soleil Ava Wizman  pages 6-10

The Blood-Brain Barrier (BBB) is a combination of various cell types that form a protective covering around the blood vessels of the brain, acting as a shield for the brain and its blood vessels; the BBB maintains homeostasis and the asepsis of the central nervous system. This barrier prevents damaging macromolecules such as large proteins and other blood constituents from entering. The protection-necessary nature of the barrier caused this barrier to evolve to make exogenous treatment of certain diseases difficult - overprotection of the barrier can have its advantages and disadvantages. The dysfunction of the BBB is shown to have an impact on diseases in the brain. Further research has to be done about the Blood-Brain Barrier and its uncompromising durability to get modern treatments to travel from blood to brain.

Benefits of Music on the Brain  Victoria Man  pages 11-14

This article focuses on the advantages of music on the brain; the benefits and how it can be utilized as a potential therapeutic technique due to its ability to stimulate multiple cognitive areas. Musicians or people actively involved in the field of music have to constantly rely on the learning ability of their brain, enabled by neural plasticity. Adult musicians engaging in instrumental practice have more gray matter in the somatosensory, premotor, superior parietal, and inferior temporal areas of the cortex. Greater musical expertise meant the musician had greater gray matter density in areas involved with higher order cognitive processing and auditory processing as indicated by a study. It is also related to improved memory and brain activity. Researchers believe that music enhances memory by stimulating the release of neurotransmitters and peptide hormones. Music therapy is a popular therapy which uses music activities to enhance physical and mental health of the patients. Music directly affects the brainstem structure and limbic system. More research is being done to execute music therapy.

Maternal Factors that Affect the Child's Brain Development  Alekhya Buragadda  pages 15-18

This article focuses on the different maternal factors associated with a child's brain development which should be taken into account during pregnancies in order to avoid severe dysfunctions. Maternal hypertension, premature birth and improper nutrition are some of the essential factors that may cause a hindrance as they exert the biggest influences on the brain development of a child. Ignoring such factors often leads to disorders such as preeclampsia and asphyxiation. Medications and intake of specific nutrients such as folic acid is often recommended by doctors. Vaccinations for pregnant mothers is one of the ways through
which an infant can be protected against viruses such as Zika virus that results in miscarriages or deformities. Exposure to toxins through maternal smoking often leads to the development of neurological diseases in infants. The article concludes by saying that there are indeed a lot of factors that should receive proper attention for safe pregnancies and that further studies must be conducted to encompass a well-rounded understanding of the factors that affect the newborn's brain development and certain measures the mothers can take to prevent them.

Evaluating the Effect of Pollution and the Quality of our Environment has on Mental Wellbeing

Aryan Kodali

The presence of pollutants in the air has a well-documented negative effect on the environment and on our physical health, especially respiratory and cardiovascular systems. However, their impact on our mental health is poorly understood. Some studies, which aimed to examine the effect of pollution on the well-being of people in urban settings have demonstrated a strong positive correlation between highly polluted air and a higher risk of worsening mental health. While the role of specific pollutants, such as carbon dioxide, in climate change can be directly linked to worsened physical health, its impact on our mental state is examined less vigorously. Furthermore, numerous factors that play into the quality of our environment and housing conditions are proven to influence our mental health. Research into the possible methods of improving the well-being of individuals living in highly polluted areas is especially pressing for marginalized and low-income communities, which are affected the most.

DISEASES AND DISORDERS

Huntington’s Disease: Potential RNA-based Treatments

Aleksandra Dubno

Huntington’s disease is caused by the abundant occurrence of nucleotide repeats on the gene sequence of the HTT protein, which leads to aberrant mRNA splicing forming insoluble aggregates. While the wild-type form of this protein is known to participate in embryonic development and cellular infrastructure, its mutated form can disrupt the function of the endoplasmic reticulum and numerous other proteins. This primarily damages dopaminergic neurons in the basal ganglia, which normally participate in the regulation of motor behaviour, thus resulting in symptoms such as chorea, bradykinesia and poor balance. There are numerous possible RNA-based approaches for the treatment of this disease. A method using antisense oligonucleotides capable of inhibiting the expression of the mutated protein has not been quite successful. In contrast, research into the reduction of HTT levels with RNA-based interference has brought promising results, with clinical trial studies currently being conducted.

Antisocial Personality Disorder: An Overview

Ahmed Shahab

Antisocial personality disorder (ASD) is a cluster B personality disorder, meaning it is characterized by dramatic and unpredictable behavior such as untamed aggression (due to a less active MAOA gene) or social apathy (due to lapse in activity from the brain space between the amygdala and cingulate cortex). The exact cause of the disorder is unknown, but abusive treatment during the individual’s developmental years
coupled with predisposed genetic factors are thought to play a part. Those with ASD are more likely to break laws, abuse drugs, and are numb to conditioning efforts. There is no sure treatment for ASD, but medication and psychotherapy may help tame symptoms.

Myelomeningocele: Current Knowledge and Therapeutic Horizons  
Jay Dalal  
Pages 37-43

Myelomeningocele (MMC) is the most severe and common form of Spina bifida, characterized by the formation of a sac of fluid on a newborn's back, openly exposing their spinal nerves. The disorder of MMC is failed neural tube closure in the embryonic spinal region, which results in prolonged exposure of the neural tube to the toxicity of amniotic fluid. MMC is also the main form of Spina bifida associated with malformations in brain structures and the development of hydrocephalus. MMC is traditionally treated with surgery shortly after birth, though open fetal surgery and fetoscopic repairs have been emerging as well.

What is HTLV-1 and its Significance?  
Arushi Neravetla  
Pages 44-47

Human T-cell leukemia virus type 1 (HTLV-1), a rare chronic neurological disease, is distributed around the world. Patients experience trouble walking, urinary dysfunction, and numbness in their lower limbs. This disease is associated with an aggressive lymphoma, and has a mean survival time of 8-10 months. It is transmitted through direct contact through bodily fluids - often reported among sexual partners. Currently, diagnosis practices include screening tests followed by confirmatory tests, and RIA - a sensitive technique used to measure the specific concentration of HTLV-1 antigens; most screening tests rely on immunoassays, which rely on HTLV-1 antibodies. These tests detect antibody reactions. Affected individuals are shown as asymptomatic and there is currently no treatment for this disease.

PSMA PET Scan-Targeted Therapy: A Cure for Prostate Cancer  
Reeva Kotha  
Pages 48-51

The refined Prostate-Specific Membrane Antigen (PSMA) positron emission technology (PET) Scan is a novel procedure in medicine for males with prostate cancer, the most common cause of cancer in men caused by a gradual tumor in the prostate gland. The scan is designed to detect metastatic maladies throughout the pelvis and body more accurately and efficiently. PSMA functions by detecting and locking the PSMA protein cell and then binding to the cancer cell, internalizing it and exposing it to heavy radiation. The procedure uses less radiation than CT and bone scans, but is limited by high costs and lack of dependable data.

RESEARCH

A Multi-Factored Experiment Testing the Effect of Magnitude of Change on Perceptual Ability  
Atul Venkatesh and Jeffrey He  
Pages 52-58

This article focuses on the ability and the extent of an individual to perceive changes in his/her surroundings
and the innate tendency of the brain to filter out/block out those “unwanted” information through selective vision and change blindness. This is an experimental study conducted in order to test three changes - the amplitude difference of the change, the wavelength difference of the change and the size of the objects being changed. During each trial, each participant was asked to observe their surroundings after a researcher informed them that they would be surveyed about their observations after the period of five minutes elapsed.

Data collection involved asking the participants if anything had changed about the appearance of the researcher, explicitly noting the possibility that nothing had changed at all. Data from statistical analysis showed that the more drastic the change, the more likely an individual was able to perceive that change. The article concludes by saying that results of the experiment can pave the way for research leading to future applications in the real world.
Letter From the Editors

Journal Leadership

Dear Readers,

Welcome to the second installment in the sixth season of the IYNA Journal! Whether you’re a newcomer or a returning reader, we greatly appreciate you taking the time to keep up with the latest in neuroscience. For many, classes have started; we hope to add to your educational experience with the articles that we’ve handpicked for this month’s journal.

This issue examines a broad range of topics regarding neuroscience. As in previous seasons, the articles submitted this season are consistently intriguing and eye-opening. Thanks to the readers of this journal, we are able to grow our reach and showcase the work of talented authors around the world. With that being said, here are some previews of the essays published this month:

Soleil Ava Wizman provides an overview of the blood-brain barrier, Aleksandra Dubno sheds light on RNA-based treatments that have potential applications for Huntington’s Disease, and Atul Venkatesh and Jeffrey He discuss a study that examined the extent of the brain’s adaptations in response to insignificant information, such as selective vision and change blindness.

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
Ashley Thommana - Managing Editor
Haris Rana - Head of Assembly
Ashvin Kumar - Head of Recruitment
Divyash Shah - Senior Editor
Sneha Nadella - Senior Editor
Sai Snigdha Kodali - Senior Editor
Kunal Dhirani - Senior Editor
Anca-Mihaela Vasilica - Senior Editor
Nicholas Aderinto - Senior Editor
Vedha Penmetcha - Senior Editor
Vaishnavi Kode - Senior Editor
GENERAL
NEUROSCIENCE
The Blood-Brain Barrier: An Overview
Soleil Ava Wizman

Abstract
The Blood-Brain Barrier (BBB) is a complex system of various cell types that form a protective covering around the blood vessels of the brain. It performs many essential functions, such as maintaining homeostasis and the asepsis of the central nervous system. However, disruption of these functions can induce the expression and progression of multiple CNS-related diseases. Treating CNS diseases largely depends on the permeability of the BBB—drugs must be re-engineered utilizing specific techniques to allow for their selective passage through the barrier and into the target tissue. Exploration into the functions and dysfunction of the BBB is ongoing and will hopefully answer the many questions surrounding this fascinating network.

Introduction

The brain is arguably the most complex organ in the human body, shaping the way we experience and interact with the world. To accomplish these tasks, the brain must receive large quantities of vital substances such as glucose, amino acids, and oxygen, which travel through its extensive microvasculature composed of intricately arranged veins and arteries. However, because the brain is so essential to bodily function, these vessels must be highly protected in order to prevent the entrance of any bacteria or viruses that may be circulating through the bloodstream. Enter the Blood-Brain Barrier, the allegorical “shield” of the CNS’s microvasculature.

Structure

So, what is the Blood-Brain Barrier (commonly abbreviated as the BBB)? It is a semipermeable structure made up of a complex arrangement of cells that surround almost all blood vessels in the brain. It is also the site at which exchange occurs between the blood and central nervous system. As shown in Figure 1, the first layer consists of capillary endothelial cells connected by tight junctions (TJs) that form a diffusion barrier [1]. The TJs of the endothelial cells consist of three critical plasma-membrane proteins—occludin, claudins, and immunoglobulin junction adhesion molecules (JAMs) [2].

Surrounding the endothelial layer are pericytes and astrocytes, and more specifically, the astrocytic endfeet, a part of the astrocyte cell that extends
outward to enwrap the vasculature. Pericytes are essential for the formation of the BBB in embryogenesis and regulate the formation of TJs [3]. The astrocytes provide a cellular link between the capillary and surrounding interneurons and are able to secrete several chemical agents that further induce the development of the BBB [1].

Functions

The blood-brain barrier performs various essential functions for maintaining homeostasis within the CNS and, consequently, the body as a whole. A specific arrangement of potassium, sodium, calcium, and bicarbonate ion transporters and channels keep ionic composition within the CNS optimal for neural and synaptic signaling [4]. The non-fenestrated (poreless) BBB also prevents damaging macromolecules such as large proteins and other blood constituents from entering the CNS. Because blood plasma contains a significantly higher protein concentration compared to cerebrospinal fluid, many plasma proteins—plasminogen, albumin, and prothrombin, among others—pose a threat to nervous tissue cells [5]. The BBB impedes the entry of these molecules into the CNS cells, preventing the acceleration of the cell’s natural death rate [6].

Implications in Disease

Because the BBB plays such a crucial role in maintaining homeostatic and healthy function within our brains and bodies, dysfunction of the barrier can be found in many CNS diseases [7]. Leakage of the BBB is visible in people with epilepsy under contrast-enhanced MRI [8], and BBB dysfunction itself has been shown to initiate seizures [9]. Barrier dysfunction is also an integral feature of multiple sclerosis (MS) pathology. As MS is an autoimmune disease, its progression relies on the infiltration of immune cells into the CNS to attack myelin sheaths. Thus, for leukocytes to enter the brain, they must cross the BBB [10]. Many studies support this theory of leukocyte infiltration in MS occurring because of an inherent BBB dysfunction. However, contrasting studies also show lesion formation before barrier dysfunction. The role of BBB dysfunction in MS pathophysiology has sparked controversy amongst experts known as the outside-in vs. inside-out debate—the “outside-in” paradigm proposes that once myelin-specific T-cells are activated, they then migrate across the barrier, causing both direct and indirect damage to myelin sheaths. On the other hand, the “inside-out” theory suggests that MS starts inside the CNS, prompting secondary inflammation [11]. The exact cause of MS is still unknown, but it is clear that a study of BBB dysfunction may be incredibly informative in uncovering its etiopathology.

Arguably, the most fascinating implication of BBB dysfunction in disease is its role in Alzheimer’s (AD). Several imaging studies suggest that AD patients possess much leakier barriers compared to controls, suggesting that BBB dysfunction is an early biomarker of AD [12, 13, 14]. Furthermore, immunohistofluorescence experiments show that mice given a human APOE4 allele replacement (of the apolipoprotein APOE genotype), an allele widely associated with increased likelihood of AD, show thinner vascular basement membranes, and overall reduced vascularization of the cerebrum. This suggests that the APOE4 mice experienced vascular atrophy [15]. It is still somewhat unclear whether BBB dysfunction is a cause or consequence (or both!) of AD—research
in this field is ongoing. Ultimately, the BBB plays a critical part in the formation and symptoms of multiple diseases, as well as an equally significant role in treatment.

**Significance of BBB Permeability**

As stated earlier, the BBB is selectively permeable and has evolved to restrict the entry of pathogens, toxins, and other harmful substances. Before modern medicine, the BBB’s impervious structure played a key role in preserving brain health. However, the BBB now presents an obstacle for drug developers who are hoping to design medications that will bypass the barrier. Ironically, the BBB is so successful at what it has evolved to do that it makes exogenous treatment of certain diseases difficult. Without specific reengineering, no large-molecule neuropathics (also known as biologics) can enter the brain, and over 98% of small-molecule drugs are also unable to cross the barrier [16]. A select few can enter the brain via lipid-mediated free diffusion, but only if they weigh less than four hundred Daltons and form less than eight hydrogen bonds, which determines their lipid solubility [17]. Thankfully, experts have discovered a multitude of ways to modify drugs in order to allow their transport across the barrier. One commonly known method is the Trojan Horse Delivery. In this mechanism, the drug fuses with a second peptide or a monoclonal antibody designed to mimic a peptide. This antibody is the so-called Trojan horse. The Trojan Horse can then enable BBB receptor-mediated delivery so that the drug can exert its pharmacological effects on its intended targets. Small molecule drugs can also be manufactured to cross the BBB via carrier-mediated diffusion—a type of facilitated diffusion requiring a membrane transport protein [18].

**Future Research**

Although many advancements have been made since its discovery in 1880 by German physician Paul Elrich [19], much research remains to be done on the BBB. The “outside-in” vs. “inside-out” debate concerning the etiopathology of MS will continue, and getting to the bottom of which theory holds the most truth will be invaluable in finding a possible cure. Furthermore, much of current research focuses on the role of endothelial cells in BBB dysfunction. It would be interesting to further analyze each cell type composing the BBB, and the role they play in neurological disease. Another question that remains is the role of environment and genetics in an individual’s blood-brain barrier. How much of our BBB health is determined by our lifestyles, and how much is hereditary? Can we alter our diets to optimize BBB function? Recent studies have shown that physical exercise encourages barrier permeability, and induces anti-inflammatory effects [20, 21]. However, there is limited research on exercise’s long-term effects, and it remains unclear how and if physical activity is effective in slowing the progression of specific diseases. Finally, can BBB damage be permanently reversed? Research pertaining to this question is indubitably promising, but more corroboration is necessary to reach a definitive answer.
Conclusion

The BBB is an evolutionary wonder, providing the vast capillary networks of the brain with both physical and chemical protection. An array of cell types, including astrocytes, pericytes, and endothelium, work in conjunction to supply the vasculature with a vital defense, and the indispensable tight junctions assure that only the necessary substances permeate the CNS while toxins and plasma proteins stay out. Proper function of the BBB is so critical to our health that its dysfunction has been associated with many diseases, including Alzheimer’s dementia, multiple sclerosis, epilepsy, and more. However, its uncompromising durability makes it nearly impossible for modern treatments to travel from blood to brain. This is why BBB permeability is such a pertinent area of study in today’s day and age; if we can develop more effective ways to allow a drug through the barrier without compromising the integrity of the drug itself, it would aid in the alleviation of countless diseases.

References


Benefits of Music on the Brain

Victoria Man

Abstract

Music plays a prominent role as an art in all human societies. Humans engage with music by listening to it or producing it. When experiencing music, the human brain is affected positively. From improved academic performance to better overall health, music provides many benefits to the brain through physiological changes and changes in regular brain functions. This article delves into major advantages of music on the brain, focusing on its benefits in medical treatment.

Introduction

From listening to musical tunes to playing an instrument, music in all forms can engage multiple regions of the brain [1]. Music is transmitted in the form of sound waves. The ability of these sound waves to interact with brain waves is the basis of many research studies. From these studies, one repeated conclusion is that music aids brain and cognitive development. Listening to music and music training (music theory/performance) stimulates the regions of the brain relating to language, motor, and cognitive functions simultaneously [2]. Both ways of interacting with music ultimately benefit an individual's cognitive function, learning, well-being, and more [1][2]. Due to the researched advantages of music on the brain, scientists believe music can be used in therapeutics for treatment of Alzheimer’s Disease, anxiety, and neuropsychiatric disorders [2][3].

Greater Brain Plasticity

Neural plasticity, the ability of the brain to change neural networks based on growth and reorganization, is the basis of learning, development, skill improvement, and rehabilitation from types of trauma. It is the changes in brain function or structure that affect cognition or behavior [2][4]. Musicians that practice to master an instrument rely on the learning ability of their brain, enabled by neural plasticity. A study by Gaser and Schlaug conducted in 2003 has identified anatomical differences regarding the neural connectivity linking the auditory and motor cortices and cortices themselves between musicians and non-musicians [4].
Most of the notable effects of increased neural plasticity are seen in gray matter densities of instrumental musicians. Through the same study by Gaser and Schlaug, it was found that adult musicians engaging in instrumental practice have more gray matter in the somatosensory, premotor, superior parietal, and inferior temporal areas of the cortex (refer to figure 1). Though there were other identified regions in the brain that also had an increased gray matter volume in musicians, it was mainly the aforementioned areas that had a greater demonstration of gray matter densities. The enlargements of these brain areas have a direct relationship with the musician’s level of expertise. From Hutchinson’s study in 2003, it was determined that musicians also have larger cerebellar volume than non-musicians. The increased volume correlates with the lifelong intensity of musical practice, which is said to be due to the cerebellum’s role in cognitive and motor skill learning [4].

For example, the Heschl’s gyrus is a region of the auditory cortex linked to the ability to discriminate pitches and detect tonal patterns; this area may have more gray matter that correlates to the degree of musical achievement. In a general study investigating non-musicians, amateur musicians, and expert musicians, it was discovered that greater musical expertise meant the musician had greater gray matter density in areas involved with higher order cognitive processing and auditory processing. Through this study, it was found that increased expertise showed a decrease in gray matter density in sensorimotor function based areas, which was suggested to be caused by the increased automatization of motor skills or higher motor efficiency seen in musicians. It is concluded that anatomical changes in the brain’s auditory and motor areas significantly correlate with active instrumental music engagement [4].

Research on music and neural plasticity has been mostly focused on gray matter volume in cortices related to musical training, which may reflect increased neuronal or synaptic count. It
reflects this due to the fact that more gray matter in the brain may enable new dendrite growth and pre-existing synaptic connection disinhibition or inhibition. Over time, researchers such as Schlaug and others have investigated white matter differences (reflecting differences in volume of nerve fibres that highlight neural connectivity) between musicians and non-musicians to gain more insight on the neural connectivity in the brains of musicians. This investigation on white matter revealed that the musician’s corpus callosum, the fiber tract fundamental to communication between the brain’s hemispheres, are greater in size than those of non-musicians. The larger corpus callosum volume of musicians suggests greater communication between the right and left hemispheres as well as the lesser interhemispheric inhibition [4].

**Improved Memory and Improved Brain Activity**

Whether it is the listening to music’s pitch, tone, rhythm, harmony and melody or the performance of the music, music illustrates artistic imagery using sound. In an individual’s brain, the auditory cortex helps monitor and recognize. Thus the auditory cortex plays a role in complex brain functions such as auditory scene analysis, sound analysis, and auditory memory. Engaging with music can enhance EEG (electroencephalography) response in temporal-limbic areas, which strengthens brain functions and networks. This significantly improves brain activity as increased EEG responses improve both memory and the processing of emotions [2][5].

For the molecular biological basis of how music benefits memory, researchers believe that music stimulation can change the secretion of some neurotransmitters and peptide hormones, thereby enhancing people’s memory. In recent studies, it has been discovered that vasopressin AVP (4-8) secretion increases significantly when the brain detects music. Vasopressin AVP (4-8) can activate the mitogen-activated protein kinase (MAPK), which greatly increases the “immediate early gene” c-fos’ transcription level. C-fos has a crucial influence on synaptic differentiation and learning and memory [2].

**Growth in Music Therapy**

Music therapy is becoming increasingly popular as it continues to be developed further and practiced by more professionals [2]. It is a treatment based around medical psychology and around using music activities to enhance the physical and mental health of patients [1][2]. Through physical and physiological functions, music impacts the limbic system and brainstem structure directly. There are two types of music therapy: active and passive. Passive music therapy (also perceptual music therapy) is a treatment method where patients mainly listen to music, whereas active music therapy consists of patients actively participating in musical activities like singing or playing instruments. At present, passive music therapy is predominantly used compared to active music therapy. Studies have also shown that treatment involving music therapy in combination with drug therapy has a significant effect when treating senile depression, schizophrenia, stroke, and anxiety [2]. In regards to treating depression and anxiety, AARP conducted a survey that revealed that music listeners had better mental health and slightly reduced levels of depression and anxiety compared to people overall [1].
Conclusion

Being a musician or just simply listening to music greatly benefits the brain in different ways [1][2][3][4][5]. Greater neural plasticity is a result from prolonged instrumental music practice, which demonstrates higher brain activity [4]. From having a better attention span to having a happier attitude and stronger cognitive function, music can exercise almost all regions of the brain [1][2][3][4]. More research is being done with executing music therapy, though it is already being employed in many organization’s programs that support patients suffering from Alzheimer’s Disease [4].

References


Maternal Factors that Affect the Child’s Brain Development

Alekhya Buragadda

Abstract

Newborns around the world suffer from numerous dysfunctionalities as a result of maternal factors. To ensure that mothers can learn about these maternal factors and prevent problems with their child’s brain development, it is crucial to research these factors and their impact. By utilizing prior studies and their impact on children, this paper is written in a cumulative manner that encompasses numerous studies and data to present detailed information about the subject matter. From infectious disease to maternal choices and environmental factors, this research study incorporates major precautions that mothers are recommended to take to ensure healthy brain development for their child. For example, the amount of brain damage cases caused by preeclampsia is five to eight percent of pregnancies and a newborn exposed to maternal smoking has a head circumference 0.5 cm smaller than a regular head circumference. Preeclampsia is caused by high blood pressure in the pregnant person and smoking leaves dangerous impacts on the child’s brain development. These are two of several maternal factors that have negative impacts on a child’s brain development.

Background

From birth to the age of three, the brain had already produced more than a million neural connections per second. How fast the brain develops is based on several factors, such as genes, proper nutrition starting in pregnancy, and the child’s experience with others in the world. The type of experiences the child endures, positive or negative, can leave lifelong effects and shape the child’s development. Hindrance to the child’s development can come from pregnancy as well. For example, factors such as nutrition, infection, and stress can leave major impacts on the child’s brain development, which will ultimately affect their physical and mental development [6]. It is crucial to give attention to maternal factors that can affect the child’s development and to take precautions to prevent any sort of obstacles to the child. For preliminary knowledge, it is crucial to understand certain nutrients that doctors recommend a pregnant person take to ensure sufficient nutrients for their child. An example of a vital nutrient is folic acid [2]. Folic acid is used as a regulator for treating low and high blood pressures [2]. Mothers usually take folic acid to prevent spina bifida, which is a common birth defect in the US [3]. It translates to “split spine” in Latin because the backbone that connects the spine is incomplete in its formation, leading to physical and neurocognitive issues. Furthermore, because folic acid also regulates blood pressure, it prevents mothers from being affected by preeclampsia [3]. Numerous diseases can affect a child’s brain development, but most of these can be prevented. This leads to the scientific question: What are the maternal factors that
affect the child’s brain development, and how can the negative impacts be prevented? If the mother endures extensive stress and improper nutrition, it will cause a hindrance to the child’s brain development. Stress and improper nutrition are common factors that harm one's health, therefore, it can be hypothesized that these are the factors that exert the biggest influence on a child’s brain development.

Factors That Impact Child’s Brain Development

Numerous disorders can be formed from a variety of factors that affect the development of the infant’s brain. One such disease is asphyxiation, which is caused by the deprivation of oxygen during birth. One of the maternal factors that trigger asphyxiation is maternal hypertension and preterm birth. Premature births have a greater risk of serious neurological disabilities or, in severe cases, death. Therefore, mothers must learn about the warning signs and know how to prevent premature births. To further ensure the prevention of asphyxiation, mothers should take certain medications, such as barbiturates, that also reduce the risk of infant brain injury [4]. Another disease that can affect the development of the infant’s brain is preeclampsia [4]. This is the condition in which a pregnant mother has high blood pressure and high levels of protein in her urine [4]. Preeclampsia affects five to eight percent of pregnancies, which results in severe effects on both the child and the mother [4]. This disease can ultimately cause cerebral palsy in the child and malfunction of the mother’s vascular system [4]. To prevent this illness, mothers should control their blood pressure by using medications and intaking certain nutrients, such as folic acid.

The mother’s choices are another factor that affects the child’s neurological development. Through various papers, researchers found that it is beneficial to her and her baby when a mother receives vaccinations. Mothers being protected from infections ultimately leads to infants' protection. For example, the baby’s brain can be infected with the Zika virus during pregnancy [2]. This virus often results in miscarriages or babies born with defects, such as a smaller head. Therefore, mothers must take the vaccinations their doctors recommend and attend regular gynecology screenings [2]. The screens are beneficial for identifying potential dangers that affect the newborn’s brain and preventing them early on. Another choice that a mother could make that would be disastrous for the child’s brain development is exposure to toxins, including tobacco smoking and alcohol [1]. A research study found that a baby who is exposed to toxins such as nicotine, found in tobacco smoking, has a 0.5 cm smaller head circumference than a regular-sized baby's head circumference [1]. Maternal smoking has severe consequences on fetal brain development and function [1]. The nicotine affects axonal pathfinding and the formation of neurons. However, complications resulting from tobacco and drug use are not limited to head circumference and can include a wide variety of other effects (See Figure 1). Overall, each mother must make careful choices approved by their doctor to prevent any neurological diseases in their infants.

Lastly, the environmental factors that the mother is surrounded by can severely impact the child. A stress hormone, called cortisol, plays a vital role in fetal development. However, if the pregnant person is exposed to intense stress during pregnancy, resulting in intense levels of cortisol, it can disrupt the development of the unborn child’s brain [6]. These disruptions in the child’s brain
can lead to hypersensitivity to stress later in life and vulnerability to disease, due to an immune system problem. A psychiatry professor from Harvard Medical College says, “Parental stress does not cause these disorders, it creates vulnerability to them” [6]. Therefore, mothers must avoid intense stress, otherwise, the mother and the child are at risk. Similarly, proper hygiene influences the child’s nervous system [6]. The mother is in an unclean environment can lead to severe consequences, such as vulnerability to neurodevelopmental and psychiatric disorders [6]. For example, unsanitary environments usually trigger inflammatory events during pregnancy by “farming” the intestinal microbiota, which has a direct effect on the developing nervous system [5]. In conclusion, the environment in which a mother is living has a huge impact on the child’s brain.

Conclusion

Children across the world suffer from hindrances to brain development due to certain prenatal factors. If the mother has immense stress and an improper diet, there may be some negative impacts on the child’s brain development [6]. Before the research, the hypothesis was that stress and malnutrition are the two major factors that affect a child’s brain development. After conducting the research, the hypothesis was disproved because there are additional factors that also leave an impact on the child’s brain development. These include infectious diseases, maternal choices, and environmental factors. This research is crucial for mothers across the world to take certain precautions to ensure healthy brain development for their children. However, this research only contributes to current knowledge of the factors that impact the child’s brain development. There could be other minor variables that leave a negative impact on the child’s brain. For example, how does the genetic code impact brain development? Further studies must be conducted to encompass a well-rounded understanding of the factors that affect the newborn’s brain development and certain measures the mothers can take to prevent them.

References


Evaluating the Effect of Pollution and the Quality of our Environment has on Mental Wellbeing

Aryan Kodali

Abstract
There is plenty of information about the effect of air pollution on health and the environment. Air pollutants are linked to multiple health issues, from coughing to chronic obstructive pulmonary disease. Air pollutants are also known to be detrimental to our environment, being linked to both increasing temperatures and climate change. However, most of this information focuses solely on physical health or environmental science. There is limited information available about the effect of pollution and the quality of our environment on our mental well-being. We know that pollution and various pollutants and certain environmental factors are linked to an increased likelihood of diminished mental well-being. However, there is still a considerable amount of research to be done on how to improve our mental well-being despite these conditions. In spite of this, future research can focus on investigating the impact of certain pollutants on our mental health and establishing a connection between environmental factors and our mental health. We can also examine the complications of failing to research mental health implications of our interactions with the environment and pollutants.
Introduction

Pollution is known to have severe impacts on our environment and bodies. Before continuing, it is essential we understand what exactly pollutants are. A pollutant is a substance or energy introduced into the environment that has undesired effects, or adversely affects the usefulness of a resource [16]. Common pollutants include particulate matter (PM), ozone, carbon dioxide (CO2), and nitrogen oxides (NO, NO2, NO3). Pollutants such as particulate matter and ozone can exacerbate symptoms of illnesses such as asthma and chronic obstructive pulmonary disease (COPD) [1]. An elevated level of exposure to carbon dioxide quantities can increase transcutaneous CO2 levels (arterial CO2 levels measured noninvasively through sensors across one’s skin), peripheral blood circulation and influence heart rate variation [2]. Exposure to nitrogen oxides, especially NO2, can cause an array of health related issues, ranging from minor reactions from coughing, wheezing, and other minor lung function disturbances to serious conditions such as chronic pulmonary diseases such as chronic bronchitis and asthma [3]. As shown in Figure 1, there are a multitude of health issues related to various pollutants.
Furthermore, pollutants have a devastating impact on our environment. Particulate matter has been linked to climate change and can affect the nutrient cycle of nitrogen [4]. Ozone damages plants by entering stomata (leaf openings) and oxidizing plant tissue during respiration [17]. Carbon dioxide is known to increase temperatures, extend the growing season, and increase humidity. This change also causes undue stress on plants, forcing them to use more water to survive [5]. Nitrogen oxides can also be harmful to vegetation, can damage their foliage, decrease their growth, and reduce crop yields [6].

Despite having studied these pollutants' environment and biological effects, large-scale experiments have not been conducted in regards to their effects on mental well-being. This article will explore implications of these pollutants on our mental well-being and also explore different facets of these issues.
The Impact of Pollutants on Our Mental Well-being

Before discussing the impact pollutants can have on mental well-being, it is important to understand what the distinct features of pollutants and mental well-being are. As defined earlier, a pollutant is a substance or energy introduced into the environment that has undesired effects, or adversely affects the usefulness of a resource [16]. Mental well-being is health associated with emotional, psychological, and social well-being. Humans are constantly exposed to pollutants, through the burning of fossil fuels, industrial emissions, transportation, demolition and construction. In the past decade, many researchers have focused on the impacts of particulate matter on mental health. In a study which contained 12,615 urban residents between the years 2014-2015, researchers found a positive correlation between air pollution and the occurrence of mental illness. More precisely, researchers found that a one-standard deviation increase in average particulate matter concentrations (18.04 µg/m$^3$ PM$_{2.5}$) is associated with an increase of 6.67% likelihood of severe mental illness [7]. According to a similar study, increase in air pollution, decrease in air quality, and temperature variability are associated with a higher risk of mental decline in participants over a period of four years [8].

As we have previously mentioned, carbon dioxide was linked to increasing temperatures and climate change [5]. Climate change causes soil degradation, loss of agricultural productivity, desertification, loss of biodiversity, destruction of ecosystems, acidification of the oceans, and disruption of stratospheric ozone. The effects of all these are damaging to physical health, causing injuries during natural disasters, malnutrition during famines, and increased mortality during heat waves owing to complications with chronically ill patients [9]. However, there is little information about the mental health impact of carbon dioxide. Multiple studies have associated the link between an increase in exposure to pollutants such as carbon dioxide and mental illness, but they have not delved past linking the two [10]. Other studies have documented human responses to high levels of carbon dioxide and air temperature. They found that an increased level of carbon dioxide exposure leads to a decrease in cognitive performance, but did not look any further to delve into its impact on mental well-being [11].

The Impact of the Quality of Our Environment on Our Mental Well-being

Before understanding how the quality of our environment can impact mental well-being, we must understand how our environment can impact our health. High-rise housing has been found to increase the psychological wellness of women with young children [12]. But housing can also lead to negative impacts on our mental health. Poor housing quality has been shown to be linked with increased psychological distress, and insufficient daylight has been reliably associated with increased depressive symptoms.

Now that we have established the link between our surroundings and mental health, we can look at the impact our environment has on our mental health. Although there are not many studies that have examined the impact of our environment on mental well-being, a specific questionnaire-based study discovered an association between our physical environment and mental
health. The study found that the strongest correlation between mental well-being or vitality and our environment come from 5 main domains: noise pollution, over-population or over-crowding, dissatisfaction with access to open green spaces, access to community facilities, and the feeling of safety when going out [13]. Following this, the results present a dire need to find out how we can improve our mental well-being despite being surrounded by these domains.

Discussion

Throughout this article, it is made evident that there are strong correlations between our environment, pollutants, our mental health and physical well-being. Subsequently, scientists have not yet conducted experiments to find how we can maximize our mental well-being while being surrounded by these problems. Groups such as the American Psychological Association are conducting experiments to correlate symptoms to specific sources of air pollution. In 2022, the APA found that air pollution is linked to depressive symptoms in adolescents [14]. However, the organization has not gone beyond that. Future research should focus on how to maximize mental well-being despite exposure to various pollutants. It is also highly important for us to focus on improving poor environmental conditions globally while maximizing our mental well-being despite these conditions. Because poor environmental conditions tend to be more concentrated around poor and ethnic minorities [13], we need to research the health implications of these conditions so that policy makers and administrators can take action when required. Experiments could also survey the effect of hearing about climate change and the feelings of hopelessness or hopefulness associated with it. Regardless of the research topics we choose to pursue, we must take action now, for the well-being of our species as a whole.

Current Consequences and Future Implications

As stated in the past section, poor environmental conditions are often concentrated around poor and ethnic minorities [13]. There is some research that has been conducted over the effect of specific environmental conditions on certain aspects of our mental health. Moreover, research has shown that poor environmental conditions exacerbate the global burden of disease. A study in Spain found that temperature, humidity, ozone, carbon monoxide, nitrogen dioxide and particulate matter are associated with both hospital admissions and exacerbation of chronic obstructive pulmonary disease (COPD) [19]. The exacerbation of the global burden of disease disproportionately impacts ethnic minority communities, as more minorities are situated in areas with poor environmental conditions.

Another study compared the link between pollution and mental health in cities compared to rural areas. The researchers found that social risk factors for those living in urban areas included concentrations of low socio-economic status, low social capital, and social segregation [20]. The researchers found that living in poor or deprived neighborhoods was associated with a greater risk of poor mental health conditions, such as depression or schizophrenia. A similar study conducted in Turkey found that living in deprived neighborhoods was likely to increase the chance of mental
illness [21]. Another study conducted in India found that adverse conditions (e.g. living in very poor neighborhoods in slums) was linked to mental health disorders [22].

A study conducted in the United States found that exposure to particulate matter during pregnancy was linked with increased depressive and anhedonia symptoms, particularly in Black women [23]. Across the world, the list of diseases more commonly associated with poor and ethnic minorities grows longer and longer.

Globally, researchers have shown a plethora of conditions and illnesses to be increasingly common in poor and ethnic communities. However, the link between exposure to poor environmental conditions, mental health, and what it means for poor and ethnic minorities has not been deeply investigated. Poor environmental conditions could be associated with poor cognitive performance and neuropsychiatric disorders, demonstrating why poor environmental conditions worsen disease in people from these socio-economic sections of society. Regardless of what exactly poor environmental conditions mean for mental health, researchers should immediately begin investigating the link between poor conditions and mental health. Research can be conducted over the analysis of causal relationships between mental health and socio-ecological factors and environmental factors. Research could also be conducted over the importance of environmental resources and neighborhood resources (e.g. parks and green spaces) and mental health. It is essential that we pursue research about these different problems to better understand how to protect our mental health. As previously stated, regardless of the research topics we choose to pursue, we must take action now, for the well-being of our species as a whole.

References


Huntington’s Disease: Potential RNA-based Treatments

Aleksandra Dubno

Abstract
Huntington’s disease (HD) is an autosomal monogenic dominantly inherited neurodegenerative disease. It was first identified in 1872 by George Huntington, who described a case of hereditary chorea. While currently incurable, Huntington’s is perhaps one of the most treatable diseases due to its known monogenic character and full penetrance [1]. It provides a unique research opportunity to discover treatments that may also be effective against other neurodegenerative diseases such as Alzheimer’s or Parkinson’s. One of the most recent innovative approaches to treatments for HD is ribonucleic acid (RNA)-based technologies.

Onset

Huntington’s disease is caused by a CAG triplet repeat expansion on chromosome four in the gene coding for huntingtin (HTT) [1]. On a normal chromosome, the trinucleotide, as mentioned above, coding for the amino acid glutamine, occurs between 10-30 times. In contrast, the repeat is expanded to at least 36 copies on an affected chromosome [2]. The disease is also inherited with age-dependent penetrance, which has a strong inverse correlation with the length of the polyglutamine expansion [2]. The repetition also accounts for 50-70% of the variance in the age of onset due to the number of repeats increasing from generation to generation [1][3]. The mean age of onset is approximately 40 years, with death usually occurring 15-20 years after onset [4].

Pathology

HTT is considered to be a large, cytoplasmic protein composed mostly of α-helical segments and consisting of repeating units called HEAT repeats [3]. It also contains an N-terminal domain with an extensive polyglutamine (polyQ) stretch on exon 1 [3][6]. Toxic N-terminal fragments may then be created via aberrant splicing of mRNA, where the expanded polyQ region causes incomplete pre-mRNA splicing of exon 1 to exon 2 [3][6]. The resulting mRNA has a stop codon after exon 1, which leads to the translation of only that fragment [6]. This cytotoxic variant is referred to as mutant huntingtin (mHTT) [6].
The self-initiated aggregation of mHTT is dependent on the polyQ expansion length [6]. The protein aggregates spontaneously and may form different structures, including oligomers and fibril-rich inclusion bodies (IB) [6]. The oligomeric aggregates of mHTT are soluble and may be found in the cytoplasm and the nucleus of the cell [6]. Meanwhile, the IB aggregates are insoluble, primarily spherical, and made of fibrils formed from tightly packed mHTT proteins [6]. Both aggregates can expand via interactions between the polyQ regions and elongate into fibrils by adding new monomers [6]. Fibrils can also recruit wild-type HTT (wtHTT), which naturally does not form fibrillar structures [6].

The function of wild-type huntingtin (wtHTT), the non-disease-causing form of the protein, is not completely understood; however, it is known to be essential for normal embryonic development, having an anti-apoptotic effect [6][7]. wtHTT is also known to perform numerous roles such as vesicular trafficking, mediation of endocytosis, vesicular recycling, coordination of cell division, and transcriptional regulation [4]. However, the formation of oligomeric and IB aggregates leads to the HTT protein losing its function and may also dysregulate the function of several other vital proteins [6]. Soluble mammalian oligomers have been shown to interact with up to 800 proteins, altering vital cellular functions such as RNA-binding, transcription, translation, mitochondrial function, and vesicle transport [6]. On the other hand, IBs are insoluble and tightly-packed structures, which limits their interactions to approximately 80 proteins [6]. Those proteins often contain prion-like sequences, which can be more easily incorporated into the aggregate [6]. Electron tomography revealed that IBs are capable of interacting with intracellular membranes, most notably the membrane of the endoplasmic reticulum (ER), “freezing” its membrane dynamics and impairing its function [6].

Additionally, mHTT may spread its aggregating potential onto neighboring cells by traveling through lysosomal secretory pathways or tunneling nanotubes [6]. This spread leads to the formation of mHTT aggregates in healthy cells, causing the gradual derailment of their cellular functions and, finally, cell death, even in previously unaffected tissues [6].

**Symptoms**

Even though huntingtin is expressed ubiquitously in the body, it is observed at its highest level in the brain and the testes [3]. However, mHTT has the greatest cytotoxic effect in the striatal neurons of the basal ganglia [8]. The presence of mHTT aggregates leads to the disruption of synaptic function and causes mitochondrial damage and neurite retraction [9]. This causes the loss of inhibitory GABAergic spiny projection neurons (SPNs), also known as medium spiny neurons (MSNs), which comprise over 90% of all striatal neurons [8].

MSNs contribute to the cortico-basal ganglia-thalamocortical loop, which is responsible for regulating motor behavior and some cognitive processes [10]. SPNs can be subdivided into two separate types of equal proportions: D1 & D2 [10]. The D1 dopamine receptor-expressing SPNs (dSPNs) form the direct pathway and project directly into the inner globus pallidus (GPi), and the substantia nigra pars reticulata (SNr) [8]. On the other hand, D2 dopamine receptor-positive SPNs
(iSPNs) form the indirect pathway and project into the external part of the globus pallidus (GPe), which in turn sends its axons into the subthalamic nucleus (STN) [8]. The direct and indirect pathways have opposing effects on the GABAergic neurons, which comprise the GPi and the SNr [8]. These two regions form the output of the basal ganglia responsible for the inhibition of cells in the ventral anterior and ventral lateral nuclei of the thalamus [8]. Thalamic nuclei are responsible for sending glutaminergic projections to the frontal cortex forming the cortico-basal ganglia-thalamocortical loop [8]. The direct pathway inhibits the GPi and SNr, leading to an excitatory effect on the loop and facilitating motor movement execution [8]. Meanwhile, the indirect pathway has an excitatory effect on the GPi and SNr, causing the opposite effect on the thalamus and cortex and suppressing undesired movements [8].

Evidence, including post-mortem studies and PET scans, shows that D1 and D2 populations are affected differently by HD, and that D2 SPN loss potentially precedes D1 SPN loss [10]. As the disease progresses, not only does this lead to a loss of up to 25% of brain weight, but HD also has a variety of visible symptoms [6]. The disease is most famously associated with chorea, which involves spontaneous, undesired, and irregular movements [3][11]. However, it is also characterized by other motor impairments, including dystonia (a hyperkinetic movement disorder that causes sustained or irregular muscle contractions leading to abnormal repetitive movements), bradykinesia (slowness of movement), incoordination, rigidity, and poor balance [5][12][13]. Finally, HD also carries a wide range of psychiatric symptoms such as depression, anxiety, obsessive-compulsive disorder, irritability, aggression, apathy, and psychosis [1].

Currently, a multidisciplinary approach involving pharmacological and non-pharmacological interventions is required to optimize the quality of life for people affected by Huntington's disease [1]. As we advance, preventative treatments, including gene therapies, administered before the full onset of the disease and before functional impairment occurs, are the goal [1].

RNA-Based Approaches

The creation of the toxic mHTT protein variant is crucial for the development of HD. Thus, reducing its levels could prove to be a viable therapeutic option [4][6]. This can be done by blocking the production of mHTT at a post-transcriptional level through mRNA degradation or translation prevention [6]. mRNA is an easily targetable molecule, as it is easily accessible within the cell and has no repair mechanisms [6]. This approach mostly focuses on the usage of antisense oligonucleotides (ASOs) and RNA interference (RNAi) mechanisms [4][6].

Antisense Oligonucleotides

ASOs are short, synthetic, single-stranded DNA or RNA analogs that range from 18 to 30 nucleotides [2]. Having been designed to target complementary mHTT pre-mRNA, they are capable
of binding to it and may prevent protein expression in one of three main manners, depending on their bind sites [6].

Firstly, ASOs binding can recruit RNase H1 endonuclease, which causes the degradation of mHTT pre-mRNA by recognizing the RNA-DNA duplex [6]. Secondly, the oligonucleotide binding may lead to a mediated arrest of the cell’s translation machinery, as the RNA-DNA duplex is not recognized by the ribosome [6]. Thirdly, another outcome may be the altering of pre-mRNA splicing, where ASOs binding is capable of masking splicing sequences leading to the formation of a different, non-toxic variant of HTT [6]. (See Figure 1). All three pathways result in the prevention of mHTT formation; however, since ASOs are designed to be specifically targeted, they may bind to the polyQ region within mHTT mRNA, still allowing for the creation of adequately functioning wtHTT [6].

However, due to their size, ASOs are incapable of passing through the blood-brain barrier (BBB) and must, therefore, be administered directly into the cerebrospinal fluid (CSF) [4]. Once introduced, they can efficiently pass through nerve cell membranes, have a long half-life, and are effective in low doses [4]. However, this direct intrathecal administration does pose significant risks, especially considering repeated injections would be necessary for effective treatment [4]. In addition, ASO distribution is heavily dependent on CSF dynamics, and the oligonucleotides have difficulty reaching the striatum, which is the region most affected by HD [4].

In May 2021, both stage I/II and stage III clinical trials using ASOs as a treatment for Huntington’s disease were halted due to data analysis revealing the administered drugs did not provide significant improvement compared to the placebo [14]. When given more frequently, the drug even went as far as to worsen the state of the patients, increasing the size of fluid-filled cavities in the brain known as ventricles, which occur in people with untreated HD [14]. There are several possibilities as to why the tested drugs had failed to fulfill the researcher’s expectations, including the fact that the oligonucleotides may not have reached the correct areas of the brain, such as the striatum, in the proper doses [14]. Thus, therapies based on ASOs have been demonstrated not to have been the anticipated “game-changer” for HD treatment [14].
RNA Interference

RNAi-based technologies utilize endogenous cellular post-transcriptional gene-silencing mechanisms to reduce mHTT levels [6]. This occurs as small interfering RNA (siRNA) is generated via the endoribonuclease processing of double-stranded RNA (dsRNA), where the guide strand later combines with the protein part of the RNA-induced silencing complex (RISC) [6]. This then associates with the target mHTT mRNA and induces its degradation [6]. This natural process can be exploited by introducing artificial siRNA in three potentially different forms [6]. Firstly, the single-stranded siRNA molecule can be introduced into the cell directly [6]. Secondly, it may be encoded on a plasmid in a dsRNA short hairpin RNA (shRNA) [6]. Finally, it may be introduced as an artificial microRNA (miRNA) scaffold [6].

Since siRNA does not require additional processing, it may be administered directly into the cell and induce mHTT degradation via the RNAi system [6]. However, due to their structure, siRNA molecules must be modified before introduction to enhance their delivery into neurons and reduce their cytotoxicity [6]. Similar to ASOs, siRNAs are incapable of crossing the BBB and must be introduced directly into the cell via intracerebroventricular injection, posing considerable risk [6][15]. Previously performed in vivo animal model studies have demonstrated that siRNA leads to reduced IB aggregation, increased striatal neuron longevity, and decreased motor function impairments [6]. In addition, siRNA can be designed to target mHTT RNA, allowing the healthy wtHTT variant to remain undisturbed [6].

Meanwhile, shRNA is considered a preferable form of delivery as it offers a more long-lasting suppression of mHTT compared to direct siRNA introduction [6]. As siRNAs cannot cross the BBB, shRNA uses a scaffolding-based expression, reliant on viral vectors to enter the central nervous system (CNS) [4][6]. Viral vectors are non-pathogenic, non-replicating, and elicit a minimal immune response while providing the opportunity for a single administration to potentially exhibit permanent action [4][15]. shRNA is, therefore, introduced via a striatal injection of a recombinant adeno-associated virus (rAAV) vector [4]. Once internalized, the shRNA scaffold requires processing within the cell to generate siRNA and suppress the expression of mHTT mRNA [6]. Animal model studies have revealed that shRNA expression prevents the formation of mHTT aggregates, reduces mHTT levels overall, and may lead to behavioral improvements and reduce striatal neurodegeneration [6].

Finally, micro-RNA is also expressed in a scaffold-based pathway, similarly to shRNA [6]. It is also administered via rAAV vectors and is processed after internalization [6]. However, miRNA scaffolds are better tolerated within brains of varying sizes ranging from mice to sheep [6]. They are also considered safer, eliminating the unwanted effects that may come from the discarded passenger strand released during the processing of shRNA [6]. In vivo experiments demonstrate that miRNA is capable of reaching 80% of cells in the mice striatum and can spread more easily within larger brains in comparison to the shRNA [6]. Moreover, it is considered similarly effective in suppressing mHTT mRNA to the short hairpin RNA [6].
RNAi-based technologies are currently being assessed in clinical trials within the I and II stage [4]. The most famous example is the UniQure clinical trial utilizing the artificial miRNA molecule AMT-130, which began in 2020 [4]. The greatest challenge that RNA interference technologies face is that the molecules involved are incapable of crossing the blood-brain barrier [6]. Two application techniques are currently being considered: via direct injection into the brain or the CSF or via viral vectors [4][6]. Direct injections often require complex neurosurgical procedures, which increase the risk of potential complications and may require repetitions to ensure constant suppression of mHTT expression [6][15]. On the other hand, the usage of viral vectors decreases invasiveness and may offer more long-term benefits; however, once administered, the treatment cannot be retracted in case of an adverse reaction in the patient's body [6][15]. Thus, despite promising results in animal models, mRNA targeting approaches have a long way to go as HD therapeutics [6].

Conclusion

While significant progress has been made in uncovering the biochemical processes responsible for the formation of mHTT aggregates and the phenotype characteristic of Huntington's disease, much progress remains to be made for effective clinical treatments to become a viable option. All potential approaches presented here are at various preclinical stages and show great promise for targeting the HTT protein. These pathways also open the doors to future treatments for other neurodegenerative diseases caused by aggregating proteins, such as Alzheimer's or Parkinson's. However, HD presents a unique research opportunity due to its known monogenic nature and straightforward aggregation process giving us the chance to eliminate all similar conditions in the future.

References


Antisocial Personality Disorder: An Overview
Ahmed Shahab

Abstract
Antisocial personality disorder (ASD) is a cluster B personality disorder that affects a person’s ability to empathize with others and increases their proclivity for violence. Although the exact cause of ASD is unknown, genetics and environment are known to play a factor. Childhood abuse increases antisocial tendencies. Those with ASD are more likely to have problems with alcohol, break the law, and are unable to learn from their mistakes. There are seven criteria in the DSM for diagnosing ASD and a person must meet three of them in order to be diagnosed. There is no widely effective treatment for ASD; however, a mix of psychotherapy and medication may help. Those with ASD have a less active MAOA gene which has been correlated with an increase in aggression. They also have decreased activity in the areas of the brain stretching from the cingulate cortex to the amygdala, which may explain the callousness associated with ASD.

What is Antisocial Personality Disorder?

Antisocial Personality Disorder (ASD) is a personality disorder that is characterized by a disregard for the feelings of others and the inability to show remorse or guilt for one’s actions. Individuals with this disorder tend to use their charm to manipulate others, show little or no remorse when harming others, and be consistently irresponsible [1].

Antisocial Personality Disorder is also one of ten personality disorders identified in the Diagnostic and Statistical Manual of Mental Disorders, DSM; this manual divides personality disorders into three clusters: A, B, and C. Antisocial Personality Disorder fall into cluster B, which is known as the dramatic and unpredictable cluster [2].

The difference between psychopathy and ASD is a source of debate for psychiatrists and neuroscientists. Some argue that psychopathy is simply a pop culture term, while others argue that it is a medical term that the DSM is yet to acknowledge. For the purposes of this article, psychopathy will be regarded as an extreme manifestation of ASD as the symptoms are so similar that differentiating them would be pointless. However, the focus of this article will be on ASD.
Causes

The exact cause of ASD is unknown; however, it is known that both genetic and environmental factors contribute to the development of ASD. The level to which genetics plays a role is unclear, and is estimated to range from 30–68% [3].

As for environmental factors, there are two main contributors to ASD. The first is childhood abuse. A study on the effects of abuse on children found that the prevalence of ASD among children who had been physically or sexually abused was two to four times higher than normal, and for children who suffered regular physical or sexual abuse, it was two to seven times higher than normal [4].

The second contributor is childhood psychopathology. The diagnosis of disorders such as Attention-Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, and Conduct Disorder all increase the likelihood of frequent antisocial behavior seen with antisocial personality disorder [3].

The role between genetics, environment, and how it affects the brain can be seen in Figure 1.

Symptoms & Diagnosis

The DSM’s criteria for ASD states that an individual must display “A pervasive pattern of disregard for and violation of the rights of others, occurring since age 15 years, as indicated by three (or more) of the following:"

1. Failure to conform to social norms concerning lawful behaviors, such as performing acts that are grounds for arrest.
2. Deceitfulness, repeated lying, use of aliases, or conning others for pleasure or personal profit.
3. Impulsivity or failure to plan.
4. Irritability and aggressiveness, often with physical fights or assaults.
5. Reckless disregard for the safety of self or others.
6. Consistent irresponsibility, failure to sustain consistent work behavior, or honor monetary obligations.
7. Lack of remorse, being indifferent to or rationalizing having hurt, mistreated, or stolen from another person [2].

The best way to characterize those with ASD is that they do not view people as humans. They view them as a means to an end. They are often incapable of forming strong emotional bonds with others. They are willing to lie, deceive, or manipulate anyone to get what they want.

Figure 1: This diagram shows the interplay between a person’s biology and their social environment. [5]
ASD also leads a person to seek out activities that they find pleasurable, like drinking. Several studies have been done on alcohol addiction and its correlation with ASD. These studies have shown that 70-90% of those with ASD also have trouble with substance abuse at some point in their life. This number is high in part because those with ASD do not value advice or guidance from friends and family [6].

Those with ASD are also more likely to have run-ins with the law. A survey of 320 incarcerated offenders revealed that 35.3% of them had ASD, which is significantly higher than the prevalence of 1-4% among the general population. This survey also confirmed findings that those with ASD are more likely to have substance abuse issues. Additionally, it found that those with ASD were at higher risk for self-harm, suicide, and had a lower quality of life [7].

It is also known that those with ASD have difficulty, or are sometimes incapable of, learning from their mistakes. In an Australian study, researchers tracked released convicts who had an ASD diagnosis and found that they were more likely to be reconvicted and reincarcerated following their release [8].

Treatment

There is no effective treatment for ASD. Most of the time people with ASD do not believe that they require help, so they will resist seeking a mental health expert. They will also blame their actions on others. Despite this, a mix of psychotherapy and medication can help a person. In psychotherapy a patient may go through anger management and treatment for alcohol misuse. For medication, since there is no FDA-approved drug, a psychiatrist will prescribe medicine that is taken by those with depression or anxiety [9].

Although there is a lack of effective treatment, those with ASD can still reduce their symptoms by contacting a psychiatrist.

What Is Happening in the Brain?

Although it is unclear exactly what abnormalities in the brain produce antisocial behavior, one theory relates to MAOA, the warrior gene. MAOA, or monoamine oxidase A, is the gene that produces MAO-A, an enzyme responsible for breaking down serotonin. MAOA deficiency or a low-activity MAOA gene has been associated with antisocial behavior and violence. [10] Removing the MAOA gene in animals also increases aggression. In an experiment in which mice had their MAOA gene disrupted, the mice exhibited aggressive behavior [11]. The warrior gene also explains why more men have ASD than women. Since MAOA is found on the X chromosome, females have two “chances” to get a functioning MAOA gene. Thus, antisocial behavior will be more prevalent in men because they have only one X chromosome.

While the warrior gene may explain the propensity for violence, it does not explain the lack of empathy that is characteristic of those with ASD. PET scans of several convicted murderers show
that they have less activity in their orbital cortex and the loss of activity continues from the
cingulate cortex to the amygdala. These systems make up the limbic, or emotional, system of the
brain. Lack of activity in this area may explain the callousness often seen in those who exhibit
antisocial behavior [12].

Concluding Thoughts

Understanding the inner workings of those that appear to lack basic regard for humanity is
essential because these discoveries will impact fields such as law, philosophy, and criminology.

References


Myelomeningocele: Current Knowledge and Therapeutic Horizons
Jay Dalal

Introduction

Spina bifida is a congenital malformation distinguished by a split (bifid) spinal column. Myelomeningocele, the most severe yet common form of spina bifida, is characterized by the formation of a sac on the newborn’s back that exposes the baby’s spinal nerves openly. Even with rigorous evidence-based surgery, myelomeningocele continues to overwhelm both families and surgeons. Myelomeningocele is associated with high rates of morbidity, including motor and sensory deficits, and orthopedic defects, which results in further financial and social stress. This review encompasses recent discoveries in our understanding of the categorization and epidemiology of spina bifida, and Myelomeningocele’s pathophysiology, screening/diagnosis, and treatment options.

Clinical Definitions and Categories

Spina bifida is a neural defect characterized by a split spinal column. It is congenital, meaning that it is present from birth. When the neural tube (an embryonic structure that later develops into the spine) does not fully close, the backbone that protects the spinal cord cannot form properly, leading to damage to the spinal cord and surrounding nerves. The degree of physical and intellectual disabilities depends on the size and location of the opening, how the spinal cord and nerves are affected, and the period of gestation in which the defect develops.

Spina bifida is clinically divided into 3 different forms (Figure 1). Myelomeningocele (MMC), the most common yet severe form of spina bifida, occurs when a sac of fluid containing exposed nerves forms along the back of the neonate. MMC leads to moderate/severe disabilities, particularly neurocognitive defects, leg weakness, and bowel dysfunction. Meningocele, similar to MMC,
is characterized by a sac of fluid on the baby’s back. However, this sac does not contain any exposed nerves or spinal cord, minimizing the severity of disabilities and complications. Spina bifida occulta, also known as closed spinal dysraphism, is the least severe type of spina bifida. In this case, a small gap occurs in the spine, but no opening or sac forms on the back. Because spina bifida occulta does not usually cause disabilities, diagnosis is often delayed until adolescence or adulthood [1].

**Epidemiology**

Many epidemiological reports often lump spina bifida with related conditions in the larger group of neural tube defects (NTDs). NTDs encompass any error that develops in the neural tube, not just failure of closure[2]. However, spina bifida is the most common congenital defect, so statistics of NTDs often reflect statistics in spina bifida [2]. This includes the following presented data. NTD cases have high global variability, ranging from 0.3 to 199.4 cases per 10,000 births nationally, with 80% of prevalence being greater than 6.0 cases per 10,000 births (Figure 2) [2]. In addition, within countries, differences in racial and ethnic groups have been observed [1]. In the US, for instance, compared to non-Hispanic whites, Hispanics tend to have a higher incidence of spina bifida while African-Americans tend to have lower numbers [1].

<table>
<thead>
<tr>
<th>Region</th>
<th>Median Prevalence of NTD births per 10,000 live births</th>
<th>95% CI</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southeast Asia</td>
<td>6.76</td>
<td>(5.77, 7.73)</td>
<td></td>
</tr>
<tr>
<td>Southern Asia</td>
<td>31.96</td>
<td>(21.51, 42.12)</td>
<td></td>
</tr>
<tr>
<td>East Asia</td>
<td>19.44</td>
<td>(15.46, 23.41)</td>
<td></td>
</tr>
<tr>
<td>Western/Central Europe</td>
<td>8.63</td>
<td>(6.56, 10.47)</td>
<td></td>
</tr>
<tr>
<td>Easter Europe and Central Asia</td>
<td>9.92</td>
<td>(7.6, 12.24)</td>
<td></td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>15.35</td>
<td>(12.30, 18.33)</td>
<td>Median without Folic Acid Fortification: 22.89 cases per 10,000 births</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median with Folic Acid Fortification: 7.78 cases per 10,000 births.</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>12.61</td>
<td>(8.73, 16.82)</td>
<td>Median without Folic Acid Fortification: 15.27 cases per 10,000 births</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median with Folic Acid Fortification: 9.05 cases per 10,000 births.</td>
</tr>
<tr>
<td>Australasia</td>
<td>11.40</td>
<td>(10.45, 13.04)</td>
<td>Folic Acid Fortification is implemented in wheat flour, but not rice or other grain products.</td>
</tr>
<tr>
<td>Northern Africa and Western Asia</td>
<td>17.45</td>
<td>(15.56, 21.46)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Median Prevalence of NTD births across various global regions [2]
were mildly deficient in selected nutrients, particularly folic acid [6]. Multivitamin supplementation was tested in clinical studies and was proven to be beneficial in preventing NTDs.

Concerns about the effectiveness of voluntary supplements have led to mandatory folic acid fortification (addition) to cereal grain products, thus reducing NTD rates by 25%. Mandatory implementation in other countries, particularly Chile, Costa Rica, and Saudi Arabia, has been associated with reductions > 50% [8]. Countries without mandatory folic acid fortification generally have 1.0 - 1.7 more cases per 10,000 births than countries with mandatory folic acid fortification [4][5][9]. However, while public health campaigns for fortification remain, both the underlying mechanisms of folic acid and the reason women taking supplements or eating fortified products still suffer from NTD-affected pregnancies required further study [9][10]. Recent studies have explored the genetic variation in folate transport/metabolism and how autoantibodies may interfere with the folate receptor, obstructing folate uptake. Additionally, inositol, a molecule responsible for intracellular signaling pathways and building phospholipids in the plasma membrane, has been proven to reduce NTD prevalence in mice [12].

Pathogenesis

The mechanisms behind the fetal development of spina bifida are complex and involve multiple intricate stages during and after gestation. The primary disorder of MMC is failed neural tube closure in the embryonic spinal region, resulting in prolonged exposure of the neural tube to the toxicity of amniotic fluid [1]. Miraculously, neuronal differentiation begins with seemingly normal motor and sensory functions. However, prolonged exposure to amniotic fluid causes neurons to die, resulting in the development of MMC [1].

Understanding the embryonic development of spina bifida first required knowledge of the many processes of primary and secondary neurulation. Primary neurulation, the first phase of neurulation, occurs during weeks 3 and 4 of gestation. This process is extremely intricate in terms of the delicate fetal structures formed and their molecular processes. During week 4, the neural tube zips bidirectionally toward what will become the brain and what will become the spinal cord [1]. Spina bifida that originates from defects in the sequence of primary neurulation, specifically in the spine, and involves a sac forming outside the skin is known as open spina bifida (either MMC or meningocele). Note that failed cranial primary neurulation results in anencephaly, a separate neural tube defect [1].

Secondary neurulation occurs during the 5th and 6th weeks of gestation and involves the formation of the neural tube in the lower sacral region of the spinal cord [11]. This occurs when condensations of cells with deep adhesions and interconnections undergo a process known as canalization. Canalization is the conversion from this cell condensation to the hollow secondary neural tube [11]. Note that secondary neurulation doesn’t involve a “zipping” or closure like primary neurulation, so defects that occur from this process are skin-covered and called closed spinal dysraphism (or spina bifida occulta).

In postnatal pathogenesis, myelomeningocele (MMC) is the main form of spina bifida associated with malformations in brain structures and the development of hydrocephalus. In 90% of cases, a Chiari II malformation of the hindbrain occurs. [1]. A Chiari II Malformation is characterized by beaked midbrain and displacement of tonsils and cerebellar vermis [15]. In 70% of cases, the
medulla, a structure that connects the spinal cord to other cranial structures, is elongated at the spino-medullary junction [1]. Macrostructural assessments and radiological reviews suggest normality in the basal ganglia and other subcortical structures, a reduced volume in the hippocampus (but not amygdala), and under-development of the corpus callosum [16][17][18].

The main secondary effect of postnatal pathogenesis is the development of hydrocephalus – an obstruction/buildup of cerebrospinal fluid flow in cerebral ventricles [19]. Hydrocephalus is known to impair white matter, resulting in detrimental effects on IQ and fine motor skills starting as early as 6 months of age [20][21]. Regardless, measuring MMC-associated cognitive deficits through IQ scores is considered to lead to poor and variable reflections [1]. Children with MMC tend to preserve skills in associative processing (e.g. procedures, word reading, vocabulary, language, persist, and social activation) while developing weaknesses in motor adaptability, language, comprehension, pragmatics, and hypersociality [1]. Other sources of variability in physical defects present as a result of MMC include physiological malformations, environmental factors, and socioeconomic status [22].

Screening and Diagnosis

Prenatal biochemical diagnosis for MMC developed in the early 1970s detects an elevation of alpha-fetoprotein (AFP) in amniotic fluid samples [1]. Additionally, assays of acetylcholinesterase in amniotic fluid show diagnostic/screening capabilities [23]. However, due to a minimal but existent chance of miscarriage following amniocentesis (a procedure used to collect amniotic fluid) and the development of routine second-trimester sonographic screening for anomalies, biochemical screening/diagnosis became dated and redundant [1].

Concurrent with the development of AFP tests, ultrasound machines developed non-invasive, specific, and sensitive readings, allowing for a more accurate diagnosis of MMC and other NTDs [24]. By examining the fetal spine and brain from multiple anatomical planes during the first trimester onwards, most cases of MMC can be detected in utero. Cranial features associated with
spina bifida include a small biparietal diameter (diameter of baby’s age) and ventriculomegaly, a condition in which the brain’s ventricles are enlarged \[i\]. Additionally, identification of an Arnold-Chiari II Malformation occurs through findings of lemon and banana signs in ultrasound \[25\]. The lemon sign, a lemon shape of the skull due to inward dipping of frontal bones, is in virtually all MMC cases between weeks 16 and 24 of gestation. The banana sign, a banana shape to the cerebellum, is present in 95% of MMC-affected fetuses that were feature identified in the late 1980s and are still used today \[i\].

**Treatment: Standard of Care and Emerging Evidence**

MMC has been traditionally treated with surgery within 48 hours of birth and involves the closing of the child’s back to minimize the risk of infection through the fluid sac. On the other hand, open fetal surgery and fetoscopic remains have been emerging with promising results \[i\].

For fetuses with MMC, the clinical team must prepare for a high-risk birth by providing access to pediatric surgery services, neonatal intensive unit resources, and strong communication between the obstetrical and neonatal/pediatric surgical teams \[26\]. Currently, studies suggest that the performance of a cesarean section does not affect complications related to MMC \[26\].

A majority of babies with MMC are repaired within 48 hours of birth to preserve the exposed neural tissue and reduce the risk of infection \[i\]. In the procedure, a pediatric neurosurgeon will first remove the general sac and then redirect and protect the spinal tissue by either closing the surrounding tissue or using a graft repair (skin from another part of the body) \[25\]. During postnatal surgery, around 80% of infants develop hydrocephalus (increased fluid in cerebral ventricles), causing the need for a second operation to reduce the fluid-caused pressure \[27\]. The second operation involves the insertion of a shunt, called a ventriculoperitoneal shunt, to redirect the excess fluid \[i\]. Often, shunts have to be removed or replaced as the neonate grows.

Nevertheless, through multiple clinical trials, repair of MMC prenatally yielded more effective results than postnatal surgery \[28\]. A paradigm-changing study titled management of myelomeningocele (MOMS) involved 60 mothers with fetuses affected by MMC and lasted from 2011 - 2017 \[29\]. The results of this study proved that repairing MMC through fetal surgery improves neurological function and reduces the need for the reversal of ventriculoperitoneal shunting \[29\]. Yet, it also increases rates of obstetrical complications, creating a double-edged sword when deciding between surgery pre- or post-birth.

Although the MOMS study provided compelling insight into the prenatal repair of MMC, emerging evidence is exploring the implications of fetoscopic repair (minimally invasive fetal surgery) against fetal surgery involving a more invasive technique. A 2015 meta-analysis concluded that fetoscopic repair reduced the risk of preterm birth and uterine dehiscence, a complication whether uterine muscles become disorderly and don’t attach to the rest of the uterus properly \[30\].

**Conclusion**

MMC is a calamitous congenital defect that presents a clinically significant challenge for health care providers and a life-long physical, mental, and financial struggle for those affected \[i\]. Despite the discovery of folic acid fortification and its implementation as a public health campaign,
the mechanisms of MMC remain mostly uncertain. While sonographic diagnosis is excellent for detecting MMC, optimizing postnatal, open fetal, and fetoscopic repair is critical to preventing further complications in pregnancies. Neurosurgeons, pediatricians, and other healthcare/research professionals continue to improve preventative measures and fetal/fetoscopic repairs, bringing a promising new horizon for MMC patients.

References


What is HTLV-1 and its Significance?

Arushi Neravetla

Abstract

*Human T-cell leukemia virus type 1 (HTLV-1) is a rare and chronic neurological disease, currently being studied as a global issue. It results in painful stiffness and is also referred to as “chronic progressive myelopathy” or “tropical spastic paraparesis”. Signs and symptoms may vary with the progression of the disease, and include exaggerated reflexes, muscle contractions in the ankle, urinary incontinence (loss of bladder control), and minor sensory changes. It was first described in Jamaica in the early 19th century, but the retrovirus of HTLV-1 was only discovered in the 1980s. The discovery of the virus was considerable in creating technological advancements in understanding the immunology, cell biology, and pathology of the HTLV-1 infection. Thus, the focus on the treatment and counseling is still expanding in the progress of developing temporary solutions for HTLV-1.*

Geographic Origin of Virus

A human T-cell leukemia virus type 1, also known as (HTLV-1), is a neuroinflammatory disease that has developed in 3.8% of the US population [4]. Afflicted patients experience trouble walking, urinary dysfunction, and numbness in their lower limbs [1]. Additionally, the epidemiology shows that HTLV-1 cases are distributed around the world, particularly prevalent among Australians and the indigenous people of Brazil. HTLV-1 made its probable entrance in a recent route through the east coast of Brazil in the beginning of the slave trade from the African continent, lasting 350 years. The study of the epidemiologically closed communities of indigenous populations in Brazil, allowed tracing the most likely route of entry and the spread of the virus abroad [2].
Possible Causes

HTLV-1 is associated with an aggressive lymphoma or growing and spreading quickly, leading to a mean survival time of 8-10 months. It is the first discovered oncogenic human retrovirus, and is transmitted primarily through direct contact via bodily fluids such as semen, breast milk, and blood. Furthermore, the virus itself has been reported among sexual partners. In cases of unprotected sex, transmission rate increases by 87% [1]. The specific cause, however, is not well understood since most infected individuals fail to develop signs of the disease. Theories suggest that there is usually a direct effect of the virus on the nervous or immune systems [2]. The results of HTLV-1 lead to disordered clonal expansion of blood cells called CD4+ T lymphocytes and are infected by the virus.

Diagnosis

Current practices for the diagnosis of HTLV-1 include screening tests, followed by confirmatory tests. Most screening tests rely on immunoassays, a test that measures the concentration of macromolecules through the use of anti-HTLV-1 antibodies [1]. Confirmatory tests detect antibody reactions to specific HTLV-1 antigens, the binding matter to trigger an immune response. The various test types include the Western blot and radioimmunoprecipitation assay [1]. Western blot is used to detect a specific protein in a blood or tissue sample, using gel electrophoresis to separate the sample proteins [2]. Gel electrophoresis is a type of method used in laboratories to separate mixtures of RNA, DNA, or any proteins according to the molecular size. In theory, it enables scientists to study the stated concentrations of the protein mixture and determine if HTLV-1 is present. Finally, the separated proteins are transferred out of the gel and into the surface of the cell membrane. Radioimmunoprecipitation assay, also known as RIA, is a very sensitive technique used to measure the specific concentration of HTLV-1 antigens using antibodies that are directed against antigens in the sample tissue. In general, these tests require a long period of time, reported
up to 65 days [4]. Complications can also arise in infected individuals due to the time required for the virus to appear on tests. Such delays can be an issue depending on the severity of the disease.

**Symptoms**

Theories suggest that there is a direct effect of the virus on the nervous system or immune system [1]. However, individuals who may not experience the direct effect of HTLV-1 infection are usually asymptomatic, showing no symptoms and do not develop conditions as quickly as expected. In general, multiple severe diseases are strongly associated or thought to be caused by HTLV-1. For example, it is estimated that 10-20 million people are infected with HTLV-1 [1]. Clinical findings suggest that HTLV-1 may produce or be connected to infective dermatitis, bronchitis, rheumatoid arthritis, fibromyalgia, and ulcerative colitis. These diseases also correlate with four different subtypes of ATL (Adult T-Cell Leukemia), including: acute, lymphomatous, chronic, and smoldering. Each version has a distinct effect, with a combination of skin and bone lesions (an area of abnormal tissue), elevation of serum calcium (measures the amount of calcium), enlargement of liver, and lymph nodes (part of the immune system).

**Treatment**

Currently, no treatment has been recommended or prescribed for asymptomatic HTLV-1 infection. The treatment, hence, should focus on the HTLV-1-associated diseases, namely ATL, and screening for other such diseases. Currently, no clinical tool can accurately predict the development of the diseases associated with the HTLV-1. Given such circumstances, technological developments and advancements are paving a path for medical industries to finance and develop medications for HTLV-1.

**Conclusion**

HTLV-1 demonstrates as a prime example of a human retrovirus and the prevalence of mainly found in rural and impoverished areas demonstrates the commonality of the virus in these origins. The neurological and natural aspects of HTLV-I represent a classical presentation of immune-related diseases. Thus, it reflects the disease as a part of current discussion concerning its evolution as an infectious transmission agent. The different strains in South America, for example, demonstrate their links to small groups of people who are ineffective at controlling the disease due to poor healthcare management, allowing it to become one of humanity’s few untreatable diseases.

---

**References**


PSMA PET Scan-Targeted Therapy: A Cure For Prostate Cancer

Reeva Kotha

Abstract

Prostate-Specific Membrane Antigen (PSMA) positron emission technology (PET) Scan is a new type of nuclear medicine procedure for men with Prostate Cancer. This new procedure has improved in recent times, now able to detect metastatic diseases faster and more accurately [1]. PSMA finds and locks the PSMA protein cell and binds to the cancer cell, allowing it to internalize the cell and expose it to a lethal dose of radiation [2]. This article discusses PSMA PET Scan in the following aspects: its mechanism, application, limitations, and, finally, future scope in regards to medical findings and diagnosis.

Prostate Cancer

Prostate cancer occurs only in men, inside a walnut-sized gland that produces seminal fluid that nourishes and transports the sperm. Prostate cancer, one of the most common types of cancer, occurs when a tumor grows slowly and is confined to the prostate gland. This can result in trouble urinating, bone pain, blood in the urine, or even erectile dysfunction. The severity of this cancer depends on how quickly it is detected and how soon the treatment is started. Some of the risk factors with this form of cancer include race, obesity, genetics, and age. The exact cause of prostate cancer is unknown [3].

PSMA PET Scan

PSMA PET Scan is a new imaging technique for prostate cancer that locates cancer lesions. The PSMA PET Scan uses a new PET-sensitive drug called 68Ga-PSMA-11, which is now FDA approved, to locate the cancer lesions [4]. This scan is used for males that have been newly diagnosed and are at risk for metastatic disease, as well as for men who have been previously treated for prostate cancer, with surgery or radiation, and are at risk for persistent or recurrent disease based on a rising prostate specific antigen (PSA) level in their blood [5]. One benefit of this new scan is that it can identify cancer that is often missed by other standard-of-care imaging techniques [4]. Michael Rosenblum, a patient suffering with prostate cancer who received this experimental treatment, came back post-surgery experiencing no symptoms. He is one of many patients who have had a positive recovery upon being treated with the PSMA PET Scan [10].
Mechanism of PSMA

The PSMA PET Scan uses a radioactive dye to light-up specific regions of the body. PSMA PET scans look for areas of the body where the PSMA protein is found, showing the presence of prostate cancer cells. Once found, Ga-PSMA-11 is administered in a microgram dose, and further radiation is applied. From there, the PSMA will bind to the cancer cell and inject a lethal amount of radiation, eliminating the cancer cells [6].

Application of PSMA

The application of PSMA PET Scan is mainly to more precisely scan for prostate cancer, allowing for better treatment planning and care. It is also effective in pinpointing and eliminating tumors not only in the prostate but also all throughout the pelvis and the body in cases where the tumors have migrated. Regular CT and bone scans have a 65% likelihood of detecting the location, but the PSMA Scan has a 92% location accuracy. There is also less radiation exposure when using a PSMA scan rather than a CT and bone scan, decreasing the chances of harmful chemicals in patients with cancer [4]. In addition, this scan helps to avoid other future tests and treatments because of its effectiveness in targeting the exact location of the cancer.

Limitations of PSMA

Because this is a relatively new scan, a PSMA PET Scan does have some limitations, such as a lack of data and overall high costs. Patients who belong in the two groups, newly diagnosed men with a high risk of metastatic disease and those who have been previously treated with prostate
cancer, should be the only ones treated with the PSMA PET Scan. Others should not use the PSMA PET Scan if they are not prone to a metastatic disease [8]. The PSMA PET Scan also causes stage migration, a problem that can be encountered in clinical decision making that may inflate cancer survival rates. With more accurate data and future uses, the limitations and side effects of this treatment can be reduced [9].

**Future Scope of PSMA**

While PSMA is a groundbreaking scan with advancements in detecting metastatic diseases, there is still room for improvement in regards to gathering sufficient data and lowering high costs. However, its high accuracy rate provides an immense amount of optimism for patients suffering from prostate cancer and other metastatic diseases. In the near future, there are hopes for it to be more widely available with more accurate data altogether [9].

**Conclusion**

Prostate cancer is a devastating disease that affects 1.2 million people worldwide [11]. Given its severity, there are emerging treatments that can help reduce the chances of it returning, such as the PSMA PET Scan. There are many treatments and procedures that can be done to limit the risk of prostate cancer, but novel technology makes the detection and diagnosis of prostate cancer much easier, saving numerous lives. In addition, PSMA PET Scan can be an effective tool for reducing the chances of prostate cancer coming back in specific cases. The clinical findings for this scan, which includes its accuracy, reliability, and validity, indicate that the PSMA PET Scan is a promising tool for treating prostate cancer.

**References**


RESEARCH
A Multi-Factored Experiment Testing the Effect of Magnitude of Change on Perceptual Ability

Atul Venkatesh and Jeffrey He

Abstract
Selective vision and change blindness are adaptations by the brain to block out unwanted and “irrelevant” information. This tendency causes the brain to not pick up on the changes of certain objects around it if the change is deemed insignificant. The purpose of this study was to see to what extent an individual would be ignorant to changes around them. 40 individuals were split into 8 groups and tested. Three changes were tested: the wavelength difference of the change, the amplitude difference of the change, and the size of the objects being changed. In order to test this, participants were put into a room and given five minutes to observe their surroundings. While the participants were observing, the researchers changed a part of their appearance, varying it by changing their clothing to a different wavelength or amplitude. After the five minutes passed, the participants were tested to see if they were able to perceive a change. It was hypothesized that the more drastic the change, the more likely an individual was able to perceive that change. The results reflected the hypothesis. This experiment provided an empirical foundation for future endeavors and applications in selective vision and perceptual research.

Introduction

Human perception is a concept that is integral to understanding the mind. Throughout the course of the day, the brain perceives millions of signals from stimuli that serve as a basis for comprehension and visualization. If someone perceives an object in their surroundings, the eye plays a role in visualizing the object, following which the brain registers that object and makes the individual aware of that object’s presence. However, technologization and industrialization have led to more individuals being attached to their devices, leading to a decrease in attention span and overall perceptive ability [1]. Amidst this generation’s technological shift, change blindness and selective vision have become more prominent and are necessary to understand. Selective vision is the brain’s tendency to filter the millions of signals into a few stimuli that the brain will ultimately end up perceiving. This contributes to an individual’s tendency to not notice certain objects.
Change blindness takes selective vision to the next level. Change blindness is exhibited when an individual is unable to observe a change in their surroundings, a phenomenon that occurs often due to the brain’s tendency to filter out unnecessary stimuli. Without change blindness and selective vision, it would become impossible for the brain to process information at the required speed. While the aforementioned adaptations allow the brain to function unencumbered by distractions, they also assist in the perception of small changes in an individual’s environment [2]. This experiment seeks to understand how change blindness and selective vision apply to high school students in a classroom setting. Using the knowledge already available in academia, the experiment seeks to answer the question: “To what magnitude can a change occur for an individual to not perceive the change?”

Before getting into the experiment itself, it’s important to understand the neuroscience behind vision. The first step of vision occurs when light is picked up by photoreceptor cells, known as rods and cones, present in the retina of the eye [3]. Rods, located in the outer parts of the retina, are responsible for vision at lower light levels as well as peripheral vision. By contrast, cones, located at the center of the retina, are responsible for vision at high light levels, which allows for different colors to be perceived [4]. When rods are active at low-light levels, scotopic vision occurs and when cones are active, photopic vision occurs. As the signal, originally light, is traveling through the retina, it reaches the bipolar cells. These cells are located between the inner and outer retina, which directly extend the pathway toward the brain. From the bipolar cells, the signal travels to the ganglion cells, located on the outer edge of the retina. The signal then travels to the optic nerve, a bundle of over a million fibers that connect the eye to the brain. The optic nerve is integral to visual perception as it directly transmits the signal to the visual cortex, which converts the electric signal into a visual image. Overall, the human eye is always adapting and constantly communicating with the brain, allowing it to perceive an individual’s surroundings.

Methods

Given the multidirectional nature of perception, it was necessary to bracket between variables and controls so as to isolate the variable at interest. The three variables tested were a change in size (magnitude), a change in wavelength, and a change in amplitude. Magnitude regards altering the size of the change; for example, in the context of the procedure, this meant changing a pair of glasses (small), or a shirt (large). Wavelength refers to the visible light spectrum. In the project, this involved testing at different parts of the spectrum to observe if changes were more perceivable at a certain wavelength of light. In the experiment, a small wavelength change was represented by switching a red shirt to another red shirt and a blue shirt to another blue shirt. A change from a blue to red shirt was considered to be a large wavelength change. Amplitude refers to the brightness at a specific wavelength of light. It was tested via switching between shirts of different brightness levels. In order to separate wavelength and amplitude changes, shirts of the same hex number, identifying a singular color, but different in brightness (dull and bright) were used. The lighting, classroom, and introductory phase of the procedure were all kept constant throughout each trial. Participants were selected at random from a population of students at Lexington High School.
During each trial, each participant was asked to observe their surroundings after a researcher informed them that they would be surveyed about their observations after the period of five minutes elapsed. Data collection involved asking the participants if anything had changed about the appearance of the researcher, explicitly noting the possibility that nothing had changed at all. Each participant was asked to write down their answer on a note-card, which was then collected by the researcher. In all trials excluding the control, participants that correctly identified a change, were marked as being "correct". In the control, participants that noted that no change had occurred were marked as being “correct”. Participants who incorrectly identified the change, incorrectly identified the lack of a change, or who correctly identified the change, but also identified changes that were not present in the investigator’s appearance, were marked as being incorrect. The data was then abstracted and analyzed to evaluate each hypothesis about whether each variable had an effect on the perceptibility of a change, and if so, how large of an effect it had.

Data

![Bar charts showing change in wavelength, amplitude, magnitude, and placebo trial results.]

Statistical Analysis

This analysis can be broken down into 4 individual parts, each of which explains a different aspect of vision, and the brain's ability to perceive changes in the environment.
The first aspect is the wavelength of the shirt. Per Figure 1, when the wavelength of the object stayed at 700 nm (a red shirt was swapped out with a red shirt), only 20% of the participants were able to notice that the shirt had actually changed. There were similar results with the 450 nm wavelength tests, where two blue shirts of the same color were changed. 40 percent of individuals were able to perceive a change in the individual’s clothing. A possible hypothesis behind an inability to notice the change is that because the brain is bombarded with so many visual codes, it is impossible to register every single change in the environment. As a result, a discernible change is deemed insignificant by the brain. However, when the researcher changed from a shirt emitting a wavelength of 450 nm (blue shirt) into a shirt emitting a wavelength of 700 nm (red shirt), a change was perceived by 80% of the participants. Even though the participants may not have been actively observing the researchers’ clothing, because the change was so extreme and noticeable, the brain was able to subconsciously deem the change in clothing attire significant and as a result, the change was perceived by the participants. Thus, the following statement can be speculated from the data: as the change in wavelength of an object increases, the more likely an individual will perceive the change.

Next is amplitude. Amplitude measures the intensity or the brightness of the light emitted off of an object. As shown in Figure 2, around 40% of the participants observed a change in the appearance of the researcher when the researcher used only high intensity (bright blue) shirts or only low intensity (dark blue shirts). 20% of the participants were able to notice a change when the bright blue shirt was swapped for another bright blue shirt. Similar to the wavelength explanation, the brain categorizes both the bright blue shirt and the dark blue shirt as bright and dark respectively. As a result, when the new shirt remains the same or has a similar amplitude, the brain is not able to perceive a difference, even if the shade of the shirt changed slightly. However, if the shirt had a large amplitude change, 80% of the participants were able to perceive the change. Similar to the wavelength explanation, this is because the brain is able to recognize and deem that the change is significant enough to be noticed. Based on the data, it is fair to say that as the change in amplitude of an object becomes more extreme, an individual is more likely to perceive that change.

Next is magnitude. In this experiment, shirts and glasses were chosen as variables. The shirt was considered “bigger magnitude” and the glasses were considered “smaller magnitude”. Per Figure 3, when the researcher changed their glasses from blue to red (450 nm to 700 nm), none of the participants were able to perceive the change, as it wasn’t a noticeable change. This is especially true because glasses are out of direct eyesight whereas many people look directly at a shirt. When the shirt changed from blue to red (as seen in the wavelength trial), 80% of the participants were able to perceive the change. The individuals who did not perceive the change claimed that there was a change in the undershirt of the researcher. This fits with the above explanation because participants would be more likely to perceive a change if it is larger, more vivid, and right in front of their eyes. The data reflects the idea that as the magnitude and location of a change in an object become more extreme, an individual is more likely to observe the change.

The last dataset is the placebo data. In this situation, individuals were told that there was a possibility that a change in appearance occurred when in reality there was no change at all. Per
Figure 4, 80% of the participants correctly identified that no change occurred. Those who guessed incorrectly believed that the researchers’ shoes were the objects that changed. This fits with the earlier hypothesis that if the brain deems a change to be insignificant, then the individual is more likely to believe that no change occurred in the first place. It also showed that the participants were for the most part not swayed by the researchers’ wording.

Conclusion

In conclusion, the probability that someone perceives a change increases with the extremity of the change. This seems logical since individuals would be more likely to spot a more drastic change than a smaller change. If individuals are less likely to identify smaller changes, it is possible that many small changes in the environment could have gone unnoticed. While this may seem counterproductive to human awareness, change blindness, and selective attention broadly, actually has some evolutionary basis [5]. Change blindness allows for extended focus on certain objects. While individuals may not notice a small change in their periphery, they would give all of their focus to a bigger, more important stimulus. This proved to be useful because it developed human attention and the ability to not get distracted by every small detail. Thus while a primal human was hunting, they wouldn’t get distracted by a small noise in a nearby bush. Change blindness inhibits the outpour of information by setting a significant change that the individual will perceive. Contextualizing this theory to the study, if someone is not able to notice the change, that does not necessarily mean they are less perceptive. It just means they choose to focus on other objects. When it comes to vision, every human is unique and each eye perceives images differently. However, change blindness was and continues to be a strategy that contributes to the survival of every human being.

Future applications

There are several future applications that can use the results of this experiment as a foundation for further research. For instance, future research could examine different variables that were kept constant in this experiment. Other factors such as the length of time each participant had to study the room, the room which the participants were placed in, and the position of the participants relative to the researchers are all areas of consideration for a study that pertains to how an individual’s surroundings could affect their perceptual ability. Furthermore, areas such as the time of day, light-levels within the room, and other environmental factors could also be variables to consider for such a study.

Another future area of research could be how the position and place of the change affects perceptual ability. While this study tested the perception of the participants considering different accessories, such as clothing or glasses, this study did not test changes that were not related to the researcher. For example, a possible test in a classroom setting could change a blue book that was lying on a nearby desk to a red book and observe whether individuals could perceive such a change. Given how individuals generally face and look towards a speaker (in this study, it would be the researcher), such a study that changes an object in the surroundings would likely have a more
precise picture of the relation between peripheral vision and change blindness, as it would not rely on a pre-change image that the participants are focused on even before the experiment begins.

**Real-World Consequences**

Given selective vision’s intrinsicness to perception and stimulus processing, there are a multiplicity of real-world consequences for research involving the understanding of change blindness and selective vision. Car safety is a large area of concern. There are many areas where selective vision and restrictive stimuli processing mechanisms can endanger drivers, pedestrians, or other people in a driver’s environment [6]. Within this, there has been research specifically in cases of divided attention, which can exacerbate the effects of selective attention on drivers [7]. One recent car development in response to these risks has been the creation of proximity alert systems, which audibly warn the driver if there is a person, bike, or otherwise object within the immediate vicinity of the car. This has been designed around the notion that a driver would not be capable of having constant knowledge of their surroundings, thus placing them at risk of, for example, switching lanes and crashing into a nearby car, or backing out of a parking space and hitting a pedestrian behind the car. As such, understanding the limits of human vision and perception can help researchers develop new safety mechanisms that are best tailored to ensure the security of a car, its driver, and those in the car’s immediate surroundings.

On the other hand, change blindness research can help guide future car safety education, reducing driver overconfidence, which can contribute to decisions leading to car accidents. The risks of change blindness in intersection with driver overconfidence are documented in a study examining the relationship between the two [8]. Researchers found that, based on participant-reported data, change blindness demonstrations in two different settings both generally decreased driver overconfidence by presenting the limits of vision and perceptual ability to participants. This awareness instruction remains to be studied extensively, but further change blindness research in this intersection with car safety will be promising for effective safety education on the road. For instance, if a study found that beginner drivers were less likely to notice other vehicles or pedestrians in their sideview mirror, car safety educators could design, implement, or standardize exercises that promote increased awareness of objects in the driver’s sideview mirror. Alternatively, researchers could study how different environments (cloudy, sunny, raining, fog, at night) could affect driver awareness and whether any conditions had an effect on a driver’s focus while on the road. For policymakers, the results of this study could change how roads are designed, for example, changing street-side lamps to be brighter at night, designing road surfaces to minimize the risk of sliding cars, or mandating car manufacturers include certain driver-assistance technologies to aid drivers in conditions where their awareness may be reduced.

**Glossary**

**Bipolar cells** – neurons within the retina that act as a signaling bridge between rod and cone cells and ganglion cells.
**Ganglion cells** – neurons in the innermost part of the retina that receive visual information from the photoreceptor cells via the bipolar cells, and transmit it towards the brain.

**Optic nerve** – the nerve at the back of each eye that connects the eyes to the brain. It carries visual messages in the form of electrical impulses for the brain to process.

**Peripheral vision** – vision that occurs outside of the fovea, a spot in the retina where visual acuity is highest.

**Photopic vision** – vision that occurs at well-lit light levels. Cones are used, which allows for perception of color and greater visual acuity.

**Scotopic vision** – vision that occurs at low-light levels. Rods are used, and there is very minimal color.

**Visual acuity** – a measure of the eye’s ability to spot and distinguish details within a visual field.

---

References


Contributors Page

IYNA EDITING TEAM:

Editor-In-Chief: Annie Pan
Head of Assembly: Haris Rana
Head of Recruitment: Ashvin Kumar
Managing Editor: Ashley Thommana
Journal Artist-in-Residence Jenna Mackenroth
Senior Editors: Anca-Mihaela Vasilica, Nicholas Aderinto, Divyash Shah, Sneha Nadella, Sai Snigdha Kodali, Vedha Penmetcha, Vaishnavi Kode
Junior Editors: Angelo Bravos, Nidhi Shah, Zain Rana, Sahil Shah, Katherine Kaufman, Rashad Abdelwabab, Annika Zhou, Anika Chebrolu, SriDhanya Muppalla, Madhavan Gupta, Samantha Singh
Journalists: Shrika Vejandla, Nikhil Sadavarte, Alzbeta Namesna, Jeffrey Xu, Ambalika Basak, Ellen Seo

CONTRIBUTING AUTHORS:

Featured Writers: Soleil Ava Wizman, Aleksandra Dubno, Atul Venkatesh and Jeffrey He
Writers: Victoria Man, Alekhya Buragadda, Aryan Kodal, Ahmed Shahab, Jay Dalal, Arushi Neravetla, Reeva Kotha

IYNA BOARD OF DIRECTORS:

Chief Executive Officer: Khayla Black
Chief Operating Officer: Sofia Vaca Narvaja
Board Members: Marisol Arau, Nipun Gorantla, Lara Ressin, Allen Chau, Brian Lee, Sarah Iqbal

ADVISORY BOARD:

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