FEATURED ARTICLES

‘Music as a Viable Therapeutic Treatment Option for Alzheimer’s Disease’
- Pranav Ramesh

‘A Brief Overview of Stem Cells in Neuroscience’
- Aviral Batra

‘Why We See Faces Everywhere: The Pareidolia Phenomenon’
- Patryk Wewejt

‘Von Economo Neurons and Higher-Order Functions, Intelligence, and Memory’
- David Han

INTERNATIONAL YOUTH NEUROSCIENCE ASSOCIATION
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Letter From the Editors

Sojas Wagle, Aayush Setty, Kareena Thakur, Ashvin Kumar, Kunal Dhirani, Anca-Mihaela Vasilica, Kyle Sugita, Shyam Soundararajan, and Annie Pan

Dear Readers,

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

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

Bibek Samal explores Levodopa’s effectiveness as a treatment for Parkinson’s Disease, Jason Luo gives an overview of Huntington’s Disease, Aviral Batra explains Tic Douloureux, Saffanat Sumra covers finding clarity in psychopathy, Patryk Wekwejt tells why we see faces everywhere, and Adria Adhikary sheds some light on the role of Mutant SOD-1 in the pathogenesis of Familial ALS.

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 feel free to contact us at info@youthneuro.org. We hope you enjoy reading this issue as much as we enjoyed editing it!

Best Regards,
Sojas Wagle - IYNA Journal Editor-In-Chief
Aayush Setty - Managing Editor
Kareena Thakur - Senior Editor
Ashvin Kumar - Senior Editor
Kunal Dhirani - Senior Editor
Anca-Mihaela Vasilica - Senior Editor
Shyam Soundararajan - Senior Editor
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A Brief Overview of Stem Cells in Neuroscience

Aviral Batra

Abstract
The two defining properties of stem cells are that they can differentiate into different types of cells and replicate indefinitely. Stem cells in organisms are classified based on their presence in a stage of the developmental cycle and ability to differentiate. Some stem cells can also be genetically programmed to have greater potential to specialize and these are known as induced pluripotent stem cells (iPSC). Stem cells in the nervous system are called neural stem cells and they can be found in an organism developing in the womb but also in certain regions of the adult nervous system. The adaptability of stem cells makes them attractive candidates as therapy for neurodegenerative diseases. Stem cell therapy can be challenging in neurological illness due to the complex nature of the nervous system and the newness of the research field, but experience with projects and clinical trials is helping to overcome these barriers.

What Are Stem Cells?

Stem cells are defined by two main characteristics: they can duplicate many times and change their structure to specialise into specific types of cells of the body [1]. This makes them invaluable in research, as they can be cultured an infinite amount of times for study, and they have huge potential in regenerative medicine, as they can develop into different types of tissue [1]. Different types of stem cells found in organisms are categorized based on the stage of development they are present in and their ability to differentiate.

Totipotent stem cells are cells that can differentiate into all types of tissue in an organism, and, similar to other stem cells, can renew without limit. In humans, these are found only in the first few divisions of a zygote (a fertilized egg). After the first few weeks of a human pregnancy, a zygote develops into an embryo (an unborn human in its early developmental stages) [1]. Embryonic stem cells present here are called pluripotent; like totipotent stem cells, they can develop into almost all human tissue, but unlike totipotent cells, they cannot form placental tissue (the placenta is an organ attached to the lining of the womb that provides nutrition to a baby) [1]. The stem cells with the least capacity to differentiate are known as somatic or adult stem cells which are mainly found in adult
organisms. The name is slightly misleading as they can also be present in infants. Most of these cells are multipotent; they can also specialize into different cell types but are limited in capability as compared to totipotent and pluripotent stem cells [1].

Research has also created another type of stem cell called iPSCs. Yamanaka, a Japanese stem cell researcher and the director of Center for iPSC Research and Application, won the Nobel prize for forming somatic human stem cells with characteristics of embryonic stem cells by adding four factors that changed genetic transcription in somatic stem cells [2]. This is a significant development as it allows for the development of autologous stem cells - they belong to the person from whom they are taken, so will be less likely to be rejected by the body in the form of an immune response. It also means the advantages of embryonic stem cells can be gained without ethical issues [2]. For example, embryos are destroyed in the process of acquiring embryonic stem cells in this conventional way, but the alternative route means that the adult stem cells are procured without harm to the organism. This can allow research to occur into pluripotent stem cells without damaging potential life [2].

Neural Stem Cells

Neural stem cells are more specialised than embryonic stem cells as they form the different kinds of cells that make up our nervous system and are hence multipotent. In the developing brain, these stem cells are the precursors to our peripheral nerves and CNS which make up our nervous system. They can differentiate into neurons which carry out the processing, motor and sensory functions in our brain. They can also differentiate into glial cells which provide structural support, nutrition, and speed up the transmission of signals through nerve cells in the body [4].

It was long thought that these stem cells were only found in the embryo and that the brain was an exception to the regenerative capability of other organs (such as the liver) in adulthood. However, research has shown that there are neural stem cells that can continue to make functional neurons even in the adult mammalian nervous system. Their presence has become widely accepted in the scientific community and they are primarily located in two brain areas. Neural stem cells can

Figure 1: Top image (A) depicts human embryonic stem cells. Bottom image (B) depicts neural stem cells derived from embryonic stem cells [3].
make excitatory neurons in a part of the human brain called the dentate gyrus (specifically in the subgranular zone) which is a part of the hippocampus and is associated with forming memories. Other neural stem cells have been found in the subventricular zone on the walls of the lateral ventricles of the brain which transport cerebrospinal fluid. The subventricular stem cells are known to migrate to the olfactory bulbs at the front of the brain where they play a role in olfaction (smell) [5]. Though these are the main locations, other neural stem cells have been found in areas such as the spinal cord [5]. The discovery of neurogenesis (the production of neurons and glial cells from stem cells) in the adult brain is significant as it shows how the brain displays extensive plasticity (the brain's ability to alter its connections) and can give us insight into the ways the brain may be able to recover from illness or damage to neurons [5].

Stem Cell Therapy in Neurological Disease

Neural and other types of stem cells have an extensive capability to regenerate and specialise into nerve cells; thus showing great promise for many therapies. There are two main approaches to stem cell therapy: the endogenous approach, which involves stimulating somatic neural stem cells already present in the nervous system, and the exogenous approach, which relies on in vitro (out of the body or natural biological location) culturing of stem cells and transplantation into the affected areas. These can be used accordingly depending on the type of disease [7].

Parkinson's Disease

Stem cell therapy has been a key area of research in Parkinson's disease. There is no current cure, and drugs are mainly used to control symptoms of the illness. Parkinson’s is thought to be mainly caused by a loss of dopamine-producing cells in the substantia nigra, a part of the brain which plays an important role in reward and movement. The neurotransmitter dopamine influences pathways in the brain affecting movement which means the disease causes symptoms such as tremor and bradykinesia (slowness of movement) [8]. Stem cell therapy is aimed at replacing dopamine-producing neurons in the brain to compensate for the loss of natural ones as a result of the disease. To alter their capabilities to carry out a specific transplant role, stem cells cultured with special signalling molecules can differentiate into the desired types of cells, for example, it has long since been known that ‘sonic hedgehog’ is one of the signalling molecules involved in the differentiation of neural stem cells into dopaminergic neurons [9]. Such methods are being applied in a Japanese study where clinical specialists are attempting to treat Parkinson’s with stem cells.
Various signalling molecules and stages help to convert iPSCs into precursors to dopaminergic cells to cause them to grow into dopaminergic cells once implanted into patients with Parkinson’s [10]. The use of autologous iPSCs means that they are far less likely to be rejected, and hence immunosuppressants are not needed to control the immune response to the cells. This exogenous approach of using iPSCs in Parkinson’s is, therefore, promising [11].

**Diseases/Injuries Affecting Motor Neurons**

Another example of neurodegenerative disease with prospects in stem cell treatment is Amyotrophic Lateral Sclerosis (ALS) otherwise known as Lou Gehrig’s disease. It is a type of motor neuron disease and is characterized by a loss of nerve cells responsible for voluntary muscle movement. This damage results in the classic symptoms of ALS: weakness in muscles, slurred speech and impaired movement. Like Parkinson’s, there is no current therapy that significantly halts or reverses these symptoms [12]. In ALS, stem cell therapy to replace the lost motor neurons is difficult because these neurons form long-distance connections synapsing (connecting at a gap in between neurons where neurotransmitter signals are sent) with many other neurons and muscles. As a result, stem cell therapy is focused on producing cells that connect with motor neurones, provide support and secrete neurotrophic factors - these chemicals encourage the growth and survival of neurons [13]. An example of such a study of using stem cells for ALS showed indications of clinical benefit when neurotrophic factor releasing stem cells were implanted into the spinal cord of patients. There was a decline in the increase of their score on the ALS - Functional Rating Scale-Revised (ALS-FRS-R) which highlighted the severity of their disease at a certain time. This positive influence on the prognosis of ALS patients is to be confirmed in future clinical trials [14].

Another exciting and potential therapy for damaged motor neurons is the use of spinal cord stem cells. Only two years ago, scientists managed to procure spinal cord neural stem cells from iPSCs [15]. These can differentiate into a wide variety of spinal cells that survived for long periods. These cells also branched over long distances and innervated target structures in the body. When spine cells are damaged in a spinal cord injury (SCI), stem cells have the potential to promote regeneration of damaged pathways when placed at the site of damage. Their long survival time means that they could have a lasting impact on improving the prognosis of people with spinal cord injury of which there is no current cure and very little presence of effective therapy [15]. One might think that these properties could be utilised in diseases such as ALS, where the problem is branching and innervating long targets - these stem cells tackle exactly that. However, clinical trials using spinal stem cells in ALS are either incomplete or are due to start soon. Though there is uncertainty in the prospects for stem cell therapies in these sorts of diseases, we know that it will be a key area of research.

**Challenges for Research into Therapies**

There are certainly challenges involved in research which at present is time-consuming and highly expensive for both scientists and the patients receiving treatment. This is understandable to a certain extent as it is a relatively new field of science [16]. Furthermore, there is some risk of tumours
forming as a result of stem cell implants which is an important factor to consider especially in diseases which allow patients a normal length of life. [17]. These risks are being mitigated as the field develops, alternative cheaper and faster routes of research can be found to speed up the testing of treatments. In addition, alternative methods to mitigate biological risks are also being used. Stem cell therapies are in their development stage and despite the current challenges, continued research can allow technologies to be created more efficiently and become widely available in the future [17].

Innovation and Concerns - Brain Organoids

A new and controversial use of stem cells in neurology is the growth of cerebral organoids. In this process, stem cells can be cultured in vitro with specific chemicals to direct their growth to form a so-called ‘mini-brain’ [18]. This development has already helped in the modelling of diseases: stem can be taken from patients and cultured as iPSCs or healthy brain organoids can be inflicted with drugs to help model different diseases [19]. At present, iPSCs are being used to grow brain organoids in which there are various ‘discrete but interdependent’ [18] regions; characteristics of the human brain.

The similarities between these organoids and the brains of animals such as humans, therefore, raises some ethical issues. Could these organoids develop sentience? Have they already done so and is it, therefore, ethical to continue the research if there is a chance the organoids may suffer? [20]. Furthermore, there is the question of using animals in this research. In the future, if brain organoids are transplanted into animals to trial their impacts in an organism, how should these animals be treated if they develop human-like characteristics? [20] The ethical rules around culturing and studying neural stem cells are very hazy; technology to understand and measure the scientific aspects of consciousness and emotion in organoids is in its infancy [20].

Despite this, research into brain organoids is accelerating massively, perhaps too quickly. Hilary Putnam, an American Philosopher, once put forward a thought experiment where a scientist cruelly took out a human’s brain and placed it in a vat connected to a supercomputer [21]. The brain received input from the computer and was therefore completely unaware of being attached to it. This is hypothetical, of course, but we are far closer to this being a reality now than when this scenario was put forward. This technology can further research but is also in danger of becoming unethical if it develops at its current pace.

Conclusion
Stem cells in neurology are a different entity to other kinds of stem cells, even if they may have similar characteristics. The nervous system is the most intricate of all the body systems and the mechanics of the cells that make the system from scratch is even more complex. By studying the mechanisms that develop new cells in the CNS, scientists have been able to develop stem cells out of the body into very specific types. As a result, they have provided an opportunity for new regenerative therapies for prevalent neurological illnesses such as Parkinson’s and ALS and injuries of the nervous system such as SCIs. In addition, advancements in technology have allowed us to take research even further by modelling these diseases in in vitro ‘mini-brains.’ However, as unique and as promising as neural stem cells are, they also come with their own issues. Though certain problems have been tackled such as embryo destruction and cell rejection by the development of iPSCs, dealing with neurons means dealing with possibilities of conscience and anthropomorphic (human) emotions. Growing cells of the nervous system from stem cells has huge potential for therapy, but it is necessary to ensure that their use remains ethical. A ‘brain in a jar’ reality may seem improbable in the future, but it is important to remember that growing brain organoids in vitro must have seemed ridiculous several years ago too.

References


Microbiota of the Gut and Its Relation to the Brain: The Gut-Brain Axis

Shruthi Aravindan

Abstract

A microbiota is an aggregation or community of microorganisms. The gut microbiota performs many functions in the body, from creating essential vitamins to aiding in the digestion of complex molecules. It also plays an essential role in the Gut-Brain Axis in promoting healthy mental processes and the psyche. The connections between the gut and brain are widely researched to gain insight into treating neurological and psychological disorders that do not have specific biomarkers to target. Maintaining a healthy gut microbiota subsequently contributes to the proper psychological and metabolic processes of the body. This article encompasses the importance of the Gut Microbiota, its relation to the brain, and how to maintain its healthy state.

The Significance of the Gut Microbiota

The importance of the gut microbiota is being explored in its relation to aspects of metabolism and homeostasis. Normal gut microbiota is responsible for nutrient metabolism in hosts [1]. The microbiome as a whole refers to the collections of the microbes and the genomes in a specific environment, in this case, the gut [2]. A microbiota, while typically consisting of bacteria, also includes fungi, archaea, viruses, and protozoans, can also include microbes linked with human diseases. This is usually the case in abnormal or disrupted gut microbiota [2]. While microorganisms are often considered pathogenic, the microbes of the gut are non-pathogenic and constitute a healthy gut. The gut microbiota enhances the immune system and aids in the degradation of toxic compounds. It can also help with the digestion of some foods, breakdown of complex molecules, and manufacturing of important vitamins.
The metabolites produced by the microbes in the microbiota play a significant role in the host’s functions, fitness, and health.

The Interactions

The gut microbiota has been changing for humans. Disruptions in lifestyle, health choices, and diet have led to a large-scale shift. The interactions that exist between the microbes and within the organism as a whole, change as a result of modified gut microbiota. These interactions go beyond digestion and synthesizing vitamins. Psychology studies have proven that the gut microbiota communicates with the brain through the gut-brain axis. This means that the gut microbiota develops simultaneously with the communications along the axis. The gut microbiota has an influence over mental processes, which in turn has an effect on the metabolic activities of the body, and a healthy microbiota contributes to restoring and maintaining homeostasis [4][5].

The Gut-Brain Axis

The gut microbiota controls neurological processes and the brain controls the development of the gut microbiota [6]. This complex system entails intricate communication processes that contribute to gastrointestinal homeostasis and motivation and advanced cognition functions. It is these processes and effects that comprise the Gut-Brain Axis. Given the role to monitor cognition, emotions, immunological functions, enteric processes, and many other physiological aspects, the Gut-Brain Axis is central to a healthy state of being. The axis is composed of nerve pathways, endocrine routes, and an immunological element. If the axis is disrupted, damages to homeostasis and cognitive function may occur [6]. These facets all contribute to the interactions, relations, and communications that occur between the gut and the brain, resulting in their connection. This link means that targeting the gut microbiota will provide insight into treating neurological disorders and physiological behavior.

Maintaining a Healthy Gut

With the importance and roles of the gut microbiota and its contribution to the Gut-Brain Axis established, it is evident that maintaining a healthy gut is important to keep the balance both psychologically and metabolically. Avoiding the improper use of antibiotics is an important step, as this can lead to antibiotic resistance which kills healthy gut bacteria. Alternatively, eating foods rich in probiotics (live microorganisms in yogurt, onions, spinach, etc.) can contribute to improving the health of the gut microbiota. The composition and nature of a gut microbiota vary greatly from one person to the next, depending on factors such as diet, age, medical history, and environment. General tips to help gut microbiota flourish can be implemented to aid in a healthy lifestyle.

The Biofilm Aspect

A biofilm is a conglomeration of cells that adhere together to a surface such as human tissue. The gut microbiota follows a biofilm method of growth in which the structure, metabolic functions,
and intracellular interactions are similar to biofilms growing on a surface [7]. There are currently no effective methods to treat bacterial biofilms in humans especially because of the quorum sensing that exists between the cells in the biofilms that make them impermeable. Quorum sensing is the communication that takes place between cells in response to cell density [8]. Recent research studies have established the link between spirochetes (helical or coiled-shaped bacteria) in biofilms and Alzheimer’s disease. According to the studies, there is a relation between chronic infection from spirochetes and the progression of dementia and the atrophy of the brain [9]. In post-mortem analysis, the presence of spirochetes in the brains of Alzheimer’s patients and evidence of infection makes the link between the spirochete biofilms and Alzheimer’s clear [10]. Understanding this link and continuing research in combating bacterial biofilms can prove to be essential in developing an effective treatment for Alzheimer’s.

Conclusion

With the proliferation of bioinformatics providing more insight into the gut microbiota, advances in the field will lead to great strides in Neuroscience, Psychology, Microbiology, and Gastroenterology. Further research into the Gut-Brain Axis, specifically how their interrelations can be used to treat diseases, will provide biomarkers for psychological behavior and neurological symptoms, which have been challenging to identify and target. Biofilms are rising in their concern in causing nosocomial infections (infections acquired from hospitals), and are linked to neurological diseases. Developing methods to target these bacterial biofilms is crucial in understanding and creating treatment regimens for patients of diseases, such as Alzheimer’s. The two-way communication that is established between the gut microbiota and the brain is essential to understand psychological phenomena, human behavior and to develop treatments for diseases.

References


Psychopathy: Finding Clarity in the Grey

Saffanat Sumra

Introduction

In the 1800s, being neurodivergent was a common reason behind an individual’s exclusion from society. Today, we understand that having a mental illness is not an alienating notion, but rather a realm of neuroscience which is so complex that we often misunderstand certain conditions, resulting in massive stigma around certain mental illnesses. One particular mental disorder which has often been misunderstood, frequently portrayed as violent and deceptive, is the Antisocial Personality Disorder, also referred to as Psychopathy. In general, people have fabricated all sorts of definitions for Psychopathy, some being true while many others are guided by myths. This article shall elucidate psychopathy from a biological as well as a social standpoint and raise multiple questions over the course of its analysis.

Defining Psychopathy

In clinical terms, doctors often refer to psychopathy as being defined as Antisocial Personality Disorder [ASPD], although there continue to be arguments regarding the validity of the two being the same disorders. According to the Mayo Clinic, Antisocial Personality Disorder results when “a person consistently shows no regard for right and wrong and ignores the virtues and feelings of others. People with antisocial personality disorder tend to antagonize, manipulate, or treat others harshly or with callous indifference” [1]. In layperson’s terms, people suffering from this type of disorder are usually those who are unable to feel empathy for other people or even guilt for their harmful actions.

There are certain key symptoms shared by most psychopaths. For instance, every psychopathic individual has narcissistic tendencies such as lack of empathy, a grandiose sense of self-worth, high self-esteem, feeling entitled and arrogant, and almost always seeking validation [6]. They are individuals who do not feel remorse whenever they commit an act potentially harmful to those around them. These actions have a wide range from stealing someone’s food to setting a house on fire. Regardless of the activity, the feeling of guilt is almost always absent. Hollywood and fiction novels have often portrayed psychopaths to be similar to serial killers, assassins, or even rapists—a very narrow perspective on the condition. However, it’s likely that we are not aware of psychopaths or sociopaths who exist around us and whether assigning them the title of this disorder is the correct or ethical thing to do.
Psychopathy vs. Sociopathy

Psychopathy is often confused with Sociopathy, since both of these can be defined in terms of Antisocial Personality Disorder. However, in an interview conducted by the Medcircle, Dr. Ramani, a clinical psychologist based in California, points out the key difference between someone considered a psychopath and a person who is considered a sociopath. She says “A psychopath is born, and a sociopath is made.” While psychopathic individuals may have had remorseless and arrogant tendencies since birth, sociopaths have developed these symptoms over the years [2].

Sociopathic individuals’ circumstances render them to develop such mechanisms as a mode of survival in the arduous world that they grew up in. Sociopaths bear strong resemblances with psychopaths in terms of having a narcissistic demeanor and their poor treatment of other individuals. In fact, it is a term more commonly used throughout social media and television as well, with one of its most significant and noticeable uses being in the popular novel series and show Sherlock Holmes, where the protagonist Holmes designates himself as a “highly functioning sociopath” in order to account for his indifferent and arrogant, yet considerate attitude towards others.

Biological Explanations Behind Psychopathy

Another interesting point mentioned by Dr. Ramani was about the biological difference between someone who is a psychopath and any other ordinary person or even a sociopath. She says that psychopaths “are actually believed to have slightly different autonomic nervous systems.” Our body is mainly composed of the central nervous system (the brain and spinal cord) and the autonomic nervous system, which is responsible for functions, such as breathing, which are not in our conscious control. The autonomic nervous system is further divided into the parasympathetic and the sympathetic nervous system, the latter producing responses commonly known as the “fight or flight response”, which is triggered in times of danger or extreme anxiety [7]. For instance, when a person commits a felonious act, their sympathetic nervous system may be activated, producing symptoms such as an increased heart rate, increased breathing, and dilated pupils. A psychopath, on the other hand, does not experience this similar rush of hormones, which is why they are often able to lie on lie detector tests [8].

With regard to the genes specifically contributing to APD, behavioral genetics is rather controversial when studying personality disorders. There have been multiple real-life situations employing the existence of a genetic link to psychopathic tendencies [3]. Case in point: In 2009, an Italian appeal court decided to cut down the sentence of a convicted murderer by one year on the grounds that he had a version of the MAOA gene. This gene provides instructions for the formation of Monoamine oxidase A, or the MAOA enzyme which helps in the breakdown of neurotransmitters such as serotonin and dopamine that are vital in regulating mood and emotions [10]. Possessing an alternate version of the MAOA gene influences this regulation, promoting aggression and violence.
According to Anthony Walsh from the Criminal Justice Department at Boise State University in Idaho, making such genetic determinisms is “plain stupid”, unless the condition is one such as Down’s Syndrome, in which an individual is proven to have a mild to moderate intellectual disability and executive functioning [3]. In fact, psychopaths are believed to not just be biologically disposed with their condition—the environment that they grow up in plays a critical role in the further development of psychopathic traits, similar to how sociopaths develop antisocial tendencies.

The molecular mechanisms inside the brain of a psychopath continue to remain unclear. Previous studies suggest abnormal glucose metabolism and opioidergic neurotransmission as factors contributing to violence, which is often seen in psychopaths. A very influential study was conducted on cortical neurons and astrocytes from 6 violent offenders, three non-psychotic individuals, who were involved in substance abuse, and 6 healthy subjects [6]. Their goal was to prove that alterations between the gene expressions and immune responses of each of these individuals do exist. In terms of the different types of neurons, the study found that there was an upregulation of RPL10P9 and ZNF132, and downregulation of CDH5 and OPRD1. These aforementioned genes may be relevant to lack of empathy and remorse as past studies have established connections between the up and downregulation of these genes with how psychopaths commonly react and interact with those around them [9]. While this study does establish a connection between the abnormal genetic expression unique to the neurons in the brains of psychopaths, it was conducted on a fairly small sample size, which is inevitable due to the difficulty in acquiring data from the brains of incarcerated offenders. The experimental subjects in the study represented only a fraction of the entire spectrum of psychopathy, ranging from some very strong symptoms to being almost undetectable.

Such a broad spectrum of symptoms blurs the

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<th>Facet 1: Interpersonal</th>
<th>Factor 2</th>
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<tr>
<td>1. Glibness/superficial charm</td>
<td>3. Need of stimulation/proneness to boredom</td>
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<td>4. Pathological lying</td>
<td>13. Lack of realistic, long-term goals</td>
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<td>11. Promiscuous sexual behaviour</td>
<td>15. Irresponsible</td>
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<th>Facet 2: Affective</th>
<th>Facet 3: Lifestyle</th>
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<td>6. Lack of remorse or guilt</td>
<td>10. Poor behavioural control</td>
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<td>7. Emotionally shallow</td>
<td>12. Early behavioural problems</td>
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<td>8. Callous/lack of empathy</td>
<td>18. Juvenile delinquency</td>
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<td>16. Failure to accept responsibility for own actions</td>
<td>19. Revocation of conditional release</td>
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<th>Items that did not saturate any factor</th>
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<td>17. Many short-term marital relationships</td>
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Figure 1. The items on the PCL-R checklist are categorized by different factors and facets [11].
boundary defining who may be considered a psychopath and who may not. Are the traits laid down by the DSM really the best standard of diagnosing antisocial personality disorder? Looking back in time, a famous figure associated with the study of psychopathy was Robert Hare, a psychologist who extensively studied psychopathy and worked at the maximum-security British Columbia Penitentiary. He created the famous Psychopathy Check-List Revised or more commonly the PCL-R, for researchers back in the 1980s [5]. Even today, the checklist is considered to be the gold standard for diagnosing psychopathy and is employed by scientists and physicians across a wide range of fields from medicine and research to law and order.

Looking Ahead: Current Progress in Psychopathy Research

From the early days of executing people for exhibiting neurodivergence, to the 21st century when the nature of extreme antisocial personality remains indefinite, there is a wide scope for behavioral research in the realm of psychopathy. While the amount of time required to find clarity in the grey area of psychopathy cannot be determined yet, current studies are working towards increasing awareness about the biological and social facts behind this deceptive disorder.

References


Abstract
About 7.6% - 30% of the general population has experienced sleep paralysis, with higher instances recorded among psychiatric patients and high school to collegiate level students [1]. Defined as a state of sleep-like immobilization in individuals immediately before or after sleep, sleep paralysis can occur in isolated or reoccurring patterns. Though medical treatment options have been largely unexplored, new research and advancements in medicine have shed light on links to environmental and neurological causes while unearthing and countering many diverse historical and cultural beliefs and their dangerous portrayal of sleep paralysis [2].

History and Cultural Origins
The discovery of sleep paralysis in the clinical environment is credited to Isbrand van Diemerbroeck, a 1664 Dutch physician [3]. In his writings, the phenomenon was referred to as simply “the Night-Mare” or “Incubus”. The primary symptoms were demonic attacks and choking, with one documented encounter describing a scene of demons forcing the patient down and giant dog-like creatures constricting breathing, only for them to eventually disappear [3]. This report sparked the beginning of the medical understanding of sleep paralysis, as an “otherworldly” phenomenon —cementing the long-lasting supernatural definition (and now stigma) in Europe and other regions of the world—with graphic depictions of demons and creatures of the night capitalizing on humanity as they lay asleep. The Incubus soon grew in popularity through cultural and religious means, and soon evolved to encompass many dream-related creatures of the night, such as the succubus and night hag.

The next mention of sleep paralysis occurred 300 years later during Sudden Unexplained Nocturnal Death Syndrome (SUNDS) episodes among Southeast Asian ethnic groups in 1977 [3]. Despite relatively good health from those affected, the death rate among Laotian Hmong men from SUNDS...
rested at 92/100,000 and the Centers for Disease Control and Prevention soon declared the cause of death “unknown”[2]—a decision that remains to this day [3]. However, since the 1977 discovery of the SUNDS Laotian death rate, the belief of dab tsog, a malicious spirit that constricts breathing, “taking the breath” of its victims at night was observed among the community—sharing a resemblance to earlier European depictions.

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<tr>
<th>Geographic Area</th>
<th>Interpretation of Sleep Paralysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Americans</td>
<td>Being bedridden, being attacked by witches, or other paranormal phenomena.</td>
</tr>
<tr>
<td>Canada</td>
<td>Interpreted as a dream but can easily be affected by an individual’s cognitive attitudes.</td>
</tr>
<tr>
<td>Egyptians</td>
<td>Caused by “Jinn” which is a spiritual creature. They call it the “Jinn attack.” It is associated with extreme fear with the belief that SP may result in death.</td>
</tr>
<tr>
<td>Germany</td>
<td>Identified as “Hexendruchem” which means “witches passing”.</td>
</tr>
<tr>
<td>Japan</td>
<td>Identified as “kanashibari” (clear cognitive framework) experience where a person feels helpless in coping with the externally impinging forces on the body.</td>
</tr>
<tr>
<td>Mexico</td>
<td>It is described as “A nightmare or a dead body of someone”.</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Nigerians describe it as “visitation of an evil spirit, witches, or some form of spiritual attack.”</td>
</tr>
<tr>
<td>Thailand</td>
<td>Identified as “Phi um” which means “enveloped by a ghost”.</td>
</tr>
<tr>
<td>West India</td>
<td>Identified as kokma”, which is in a trance, during which the sleeper cannot move. It is also described as a spirit or ghost passing through one’s body.</td>
</tr>
</tbody>
</table>

Throughout history, sleep paralysis has become known in numerous cultures, each attributing a cause of religious or mythical origin (see Figure 2). Though recent research discredits these myths, a vital window is created in understanding sleep paralysis from the perspective of the affected utilizing widespread depiction of the phenomenon.

**Symptoms and Reputation**

Sleep paralysis is characterized by complete or partial loss of motion in voluntary muscles, primarily in appendages, eyelids, and the mouth with the inability to speak. In addition, patients also report a wide array of hallucinations—both hypnagogic and hypnopompic [1]. These hallucinations are the origins of numerous cultural and religious superstitions prevalent throughout human
history (see Figure 2). These hallucinations range from pitch darkness to graphic depictions of physical and sexual assault.

Instances of atonia and hallucination often create a neglected symptom, affecting patients far after episodes—fear. A sample has shown that up to 98% of sleep paralysis patients have reported instances of fear, with clinically significant levels of fear noted in 69% of participants[i]. Combined with the historical and cultural stigma, patients afflicted with periodic or isolated sleep paralysis may be less likely to report sleep paralysis cases due to fear of public opinion. Lower reports to medical physicians may have an adverse effect as they encounter sleep paralysis patients sparingly, increasing the likelihood of misdiagnosis.

Sleep paralysis is often confused with other sleep ailments, such as Exploding Head Syndrome (EHS), Nightmare disorder (ND), and Nocturnal panic attacks, due to their associations with clinical fear and origins as REM-based parasomnias (ND only) [4]. This leads to a situation where, despite the negative effects and widespread cultural knowledge of the ailment, sleep paralysis—in terms of clinical knowledge among non-sleep specialists—is lacking, with recurrent isolated sleep paralysis, a recognized sleep-wake disorder, being harder to diagnose in patients [4].

While the medical approach to sleep paralysis often lies in educating patients about the harmlessness of the ailment, if there is no underlying mental illness, the cultural and religious approach is often more “idealistic” and “calming” to affected patients. Methods ranging from elaborate rituals, changing sleep positions, or reciting passages of the Quran and Bible are readily available and receive much more attention [2].

Clinical levels of fear, in select instances, may lead to patients misrepresenting the ailment, leading to misdiagnosis or wilder expressions of panic. In a study conducted by McNally and Clancy, the claims of ten individuals reporting abduction by space aliens were linked to episodes of sleep paralysis where hypnagogic and hypnopompic hallucinations were “interpreted as alien beings” [5].

Causes, Demographics, and Factors

Sleep paralysis occurs as atonia or muscle paralysis common during the rapid eye movement (REM) stage remains as the patient regains awareness upon waking or as the patient slips into unawareness upon just falling asleep. As this occurs, sections of the brain, including the parietal lobe, amygdala, and brainstem become active and may play roles in many of the hypnagogic and hypnopompic hallucinations that patients report. Potential causes of sleep paralysis hallucinations include personal trauma, body distortion, and brainstem-induced amygdaloid complexes [2]. Sleep paralysis is common across the world, with considerably high rates among certain demographic groups and regions.

A recent systematic review found that prevalence rates are higher among students, especially those transitioning from junior high school to senior high school and college [2]. This is strongly attributed to high degrees of stress students report in the Western Hemisphere. However, students
were interestingly more likely to report fear [5]. In a study conducted on Czech university students, 69% of studied sleep paralysis students reported high levels of fear resulting from a sleep paralysis episode [6].

Psychiatric patients also experience sleep paralysis at a greater rate, with the ailment being heavily linked to narcolepsy, a sleep disorder characterized by excessive daytime sleepiness and sudden convulsions to sleep. In addition, an array of neurological ailments such as idiopathic hypersomnia, insufficient sleep syndrome, panic disorder, anxiety disorder, and post-traumatic stress disorder have been linked to sleep paralysis, with panic disorder patients having the highest rate of sleep paralysis at 34.6% [1].

A variety of environmental factors have credible links to sleep paralysis, ranging from sleep quality, where studies have revealed a strong link between sleep paralysis and insomnia symptoms [7], with sleep paralysis likely occurring with other sleep experiences such as EHS and nightmare syndrome, which it is often misdiagnosed as [8]. Stressful occupations, working during the night, jet-lag, student status, instances of childhood sexual abuse, and supine position sleeping are considered risk factors alongside substance use and medications for neurological ailments.

Females are more likely to suffer from sleep paralysis than males, and non-white ethnic groups experience sleep paralysis at a much higher rate, with individuals of African and Asian descent being most at risk according to recent studies [2]. Higher instances of sleep paralysis in patients with high stress, panic disorders, and hypertension may correlate with Asian and African statistics, as these ailments are most prevalent among these ethnic groups.

**The Future of Sleep Paralysis**

As sleep disorders become more prevalent and addressed in society, so to do new possibilities for combatting sleep paralysis and related illnesses. In terms of risk factor and prevention research, new discoveries into correlations between environment, lifestyle and sleep
paralysis may spark new, self-designed choices and pathways for reducing independent sleep
paralysis episodes for students and adults -- including career, sleep, food, and drug choices [6].

Though a definite, clinical “cure” for sleep paralysis may be far in the future [2], connections
between substances and their impacts on closely related sleep disorders show considerable promise.
Recent studies have uncovered opiates as an effective substance in reversing the powerful
drowsiness effect of narcolepsy. MRIs and additional tests performed on post-mortem heroin addicts
have revealed an average of 54% more hypocretin-producing brain cells than present in the average
human brain [10]. In addition, mice genetically engineered with narcolepsy have shown considerable
progress in alertness when exposed to morphine [10]. As cells directly responsible for wakefulness,
narcolepsy patients may have much to benefit from further research into opiates and their ability to
awaken and stimulate hypocretin-producing cells as research is quickly moving to experiment with
non-addictive alternatives.

Conclusion

Sleep paralysis is an ailment that has afflicted a substantial portion of the population since
the fifteenth century—and likely beyond. Research regarding the ailment, which affects upwards of
7.6% of the population is still in its infancy, consistently finding itself unknown among the general
public due to the prevalence of cultural and religious explanations and cures that are sought out by
those afflicted. Despite this, research has revealed a variety of risk factors, links, and connections
that show promise in debunking this public, yet mysterious phenomenon. Though a concrete cure is
not yet known, providing comfort and assurance to those affected proves to be a reliable method of
calming sleep paralysis victims, with awareness being one of the most powerful tools. Through
letting the origins of this illness be known, alongside explanations of the folk aspect and
introduction of scientific research, it is possible to reach those who may brush sleep paralysis off as
“strange, paranormal and rare” and provide reassurance of the fact that help is available and they are
not alone in this struggle.

References


The Role of Mutant SOD-1 in the Pathogenesis of Familial ALS
Adrija Adhikary

Abstract
Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder that affects and destroys the motor neurons present in the Central Nervous System. It occurs in two forms, sporadic ALS (sALS) which is non-genetic and accounts for the majority of the cases of ALS, and familial ALS (fALS) that is transmitted genetically from parent to offspring [1]. Though the aetiology of both forms of ALS remains unknown, a mutation in the gene encoding Cu-Zn superoxide dismutase-1 (SOD-1) is largely responsible for the development of fALS [2]. Recent studies on mice expressing the mutant SOD-1 gene show that they display the same symptom development as patients with ALS. This article focuses on the chronological development of the pathophysiological symptoms of fALS and the associated role of mutant SOD-1.

Introduction

ALS or Lou Gehrig’s disease is characterised by the progressive neurodegeneration of mainly the pyramidal neurons in the motor cortex, that make up the upper motor neurons, and the neurons in the brain stem and central spinal cord, that make up the lower motor neurons. The progression of the disease leads to weaker muscles, as well as, the development of atrophy.

Figure 1. A side-by-side comparison of a fluid-attenuated inversion recovery (FLAIR) magnetic resonance (MR) image of the brain of an ALS patient versus that of a control [4]
fasciculations, and hyperreflexia, the clinical manifestations of which are colloquially termed as “upper motor neuron signs” [3]. The biomarker of ALS includes reduced axonal and myelin density pointing to neuronal degeneration (depicted by the arrows in the image below) [4].

Pathophysiology of ALS

fALS, a type of ALS caused genetically, can be induced by dominantly inherited mutations in the gene coding for eukaryotic Cu-Zn superoxide dismutase-1 (SOD-1). The mutant enzyme displays a toxic gain of function [5] which has been related to structural instability, misfolding, and malfunctional enzymatic activity including disturbance of redox homeostasis [6]. A remarkable feature of the misfolded SOD-1 enzyme is its ability to propagate, almost in a prion-like manner [7]. The SOD-1 secretory pathways of the cell might be responsible for the spread of the mutation in a cell-to-cell manner, from the point of initiation [8]. It also was established in a study that expression of mutant SOD-1 enzyme affected only the motor neuron cells and not interneurons, dorsal root ganglions or GABAergic neurons [9] and induced pluripotent cells (iPSCs) from patients with SOD-1 exhibited neurofilament (NF) aggregation, as well as, axonal degeneration [10].

In transgenic mice that expressed the gene for mutant SOD-1, it was gauged that multiple processes converged to reduce both embryonic stem cell-derived (ESMN) or primary spinal (PMN) motor neurons activity by glutamate accumulation followed by calcium influxes, disturbed oxidative and nitrative mechanisms and gradual failure of mitochondrial functions [11]. However, the deletion of the mutant SOD-1 gene does not entirely prevent motor neuron death, thereby suggesting that there might be alternative apoptotic pathways involved [9]. Therefore, despite having a hazy picture of each of these pathways, the exact points where SOD-1 triggers or sustains the aforementioned events remains elusive.

Oxidative Stress

The non-mutant SOD enzyme is associated with the conversion of superoxide radicals to oxygen and hydrogen peroxide. This function is critical for cell defense against the reactive oxygen species [12]. Hence it is present in the cytosol in large concentrations, “accounting for 70–80% of the total cellular SOD activity of the cell” [13]. A study using non-invasive bimolecular fluorescence complementation (BiFC) assay in human H4 cells showed that cells expressing mutant SOD-1 were more likely to have subcellular localizations and aggregations of the enzyme which might give rise to oxidative stress [6], due to the following reason.

An important aspect of SOD-1 misfolding is the loss of structural Zn2+. This increases the tendency of the Cu2+ to accept substrates other than superoxide [12] which increases the oxidizing ability of Cu2+ thus facilitating the production of Reactive Oxygen Species (ROS) [8]. It is so seen that the active Cu2+ site of the mutant SOD-1 enzyme catalyzes the oxidation of various thiol compounds. Hence, in addition to producing hydrogen peroxide, this includes CSH and Homocysteine (Hcy) [8].
The GSH present in the cell originally acts as a cellular antioxidant. However, in the presence of minute CSH or Cysteine concentrations in the cell, GSH acts as a pro-oxidant that drives the CSH-dependent hydrogen peroxide formation by reducing Cystine back to CSH. The GSH/CSH redox circuit drains the glutathione reserves of the cell in the presence of mutant SOD-1 thereby discharging the cellular antioxidant potential [8]. This depletion enhances the oxidative stress markers, markedly decreasing mitochondrial functions, facilitating the release of cytochrome c, causing apoptosis-inducing factor (AIF) translocations, and caspase 3 activation, therefore pushing the cell to a motor neuron-cell-like apoptosis [14]. Hence, the careful analysis of the distribution of thiol compounds throughout the Central Nervous System (CNS) can be used to deduce the potential locations of Reactive Oxygen species (ROS) production.

**Nitrative Stress**

Nitric oxide (NO) functions as a major signaling molecule produced by the CNS [15]. The presence of the mutant SOD-1 enzyme causes a faulty or no decomposition of the superoxide radicals present in the cell. Under inflammation or aging or oxidative stress, these two end products come together and NO combines with the superoxide to yield peroxynitrite (ONOO-) [16]. The peroxynitrite formed is responsible for the nitration of tyrosine compounds present in the neuron [17].

The nitration of tyrosine modifies key properties of the tyrosine amino acid (i.e. phenol group pKa, redox potential, hydrophobicity, etc.) which then leads to profound structural and functional alterations and increased tendency to form aggregations in the neuron, some of which contribute to altered cell and tissue homeostasis [18]. Nitrotyrosine is also a well-known biomarker for the onset of ALS due to the inhibition of trophic factors. The continuous deprivation of the motor neuron cell of the trophic factors could trigger apoptosis through the Fas pathway [19]. This might lead to cell death through the FADD-Caspase8-cytochrome c-caspase 3 pathway or lead to the production of DAXX and more peroxynitrite. Which provides positive feedback to the system to induce more nitration of tyrosines and finally cause neuronal apoptosis [15].

**Glutamate Excitotoxicity**

Glutamate represents one of the major excitatory neurotransmitters [20] present in the central nervous system, which in higher
concentrations, is toxic to the neurons. Hence, the rapid clearance of glutamate from the synaptic cleft is achieved by EAAT2 expressed by the astrocytes [21]. The presence of mutant SOD-1 blocks this pathway of transportation of glutamine leading to a glutamine buildup in the synaptic cleft [22][1]. This is one plausible explanation for the neuronal cell death in ALS.

Glutamine toxicity is also mediated by the alpha-amino-3-hydroxy-5-methyl-4 isoxazole propionic acid (AMPA) receptors [23][1]. The mutant SOD-1 gene was found to lower the expression of the GluR2 AMPA subunit along with a modest increase in the number of GluR3 AMPA subunits [24].

The GluR2 subunit of the AMPA receptors is responsible for cellular impermeability to calcium ions. On the other hand, GluR3 AMPA subunits are responsible for increasing the calcium influx into the motor neuron. With a decrease in the number of GluR2 AMPA subunits followed by a subsequent increase in the number of GluR3 subunits, calcium influxes into the spinal motor neuron cells [23][25]. A study with wild type mice and G93A SOD-1 mutant mice showed that the activation of the Ca-AMPAs channels creates a metabolic burden that coupled with the toxic gain of function of the SOD-1 mutant enzyme ultimately contributes to cell apoptosis [22].

Mitochondrial Dysfunction

Motor neurons are particular for having a low Ca$_2^+$ buffering capacity. Therefore, the entire Ca$_2^+$ load due to the replacement of AMPA receptors needs to be buffered by the cellular mitochondria. This releases a large amount of ROS which increases the oxidative and nitrative stress of the motor neuron and promotes the influx of Ca$_2^+$ [22]. This overall positive feedback loop leads to increased glutamate excitotoxicity and commences with apoptosis.

Figure 3. The above figure shows the process of calcium buildup in the nerve cell due to the replacement of the AMPA subunits [1].

In addition, motor neurons of ALS patients show a deficiency of calcium-binding proteins, mainly calbindin-D28k and parvalbumin. On the contrary, oculomotor neurons that expressed the calcium proteins were preserved [26]. Hence selective motor neuron vulnerability occurs. It was also seen that rat astrocytes expressing the mutant SOD-1 gene had decreased oxygen consumption, led to faulty membrane potential, and lack of ADP-dependent respiratory control. This eventually caused the astrocytes to induce the apoptosis of the motor neuron cells [27][28].
An Overview of the Pathway of Progression of fALS

The three major phases of the development of ALS include initiation in the form of an initial injury. Chronic and oxidative stress, as well as aging factors, cause the motor neuron cell to upregulate certain factors like nNOS, cytokines, and Fas. This might lead to the second stage leading to dysfunction of mitochondria, amplification of nitrative and oxidative stress as well as protein aggregation and glutamate toxicity. This activates the glial cells to secrete certain factors to deal with these symptoms. It results in a positive feedback loop that upregulates the formation of peroxynitrite radicals leading to more nitrative stress, as well as, poor transportation of glutamate as well as the rapid influx of calcium. All this is directly or indirectly influenced by the mutant SOD-1 enzyme. This ultimately leads the motor neuron cell to carry out apoptosis leading to the onset of the disease.

Conclusion

Despite extensive research in the field of neurobiology, the proper causative effects of neither fALS nor sALS are properly known. Mutant SOD-1 might seem to be one aspect of the causative symptoms of fALS. However, there might be more chemical aspects of this problem than we realize. Attention also needs to be paid to the fact that whatever chemical pathway the disease takes is exclusive to the motor neurons of the CNS, thereby narrowing down the search for its chemical origins, which probably holds the key to finding its cure.

References
trophic-lateral-sclerosis/pathophysiology-of-amyo


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Abstract
Von Economo neurons, also called spindle neurons, have been studied for their link to higher intelligence and memory capabilities. This article will discuss the role of the von Economo neurons in human brains, as well as the prominence of von Economo neurons in Superagers, individuals above the age of 80 with the cognitive function of a middle-aged individual, and neuropsychiatric disorders such as autism. Furthermore, this article will describe the potential relationships that can be explored between higher intelligence and von Economo neurons with further testing and research.

Introduction
Sensory neurons, motor neurons, and interneurons makeup roughly 86 billion neurons in the brain and have a wide range of functions from movement to emotion [7]. However, a type of neuron found in humans and major primates may be able to explain how higher intelligence and memory arose. Scientist Constantin von Economo found a spindly neuron, larger than a typical pyramidal neuron, with only one dendrite. He named this neuron ‘the von Economo neuron’ or VEN [1]. The von Economo neuron was discovered in the fronto-insular and anterior cingulate cortex of the human brain [2]. The neuron has been identified in species with large brains with different genetic lineages such as dolphins, whales, elephants, and humans, which suggests a possible case of convergent evolution to support brains of bigger size [3]. Convergent evolution is defined as the process in which organisms that are not closely related independently evolve similar features [4]. The fronto-insular cortex in the human brain is responsible for “sensory processing, feelings and emotions,
autonomical and motor control, risk prediction and decision-making, bodily- and self-awareness, and complex social functions like empathy” [5]. The anterior cingulate cortex is responsible for empathy, emotion, decision making, and impulse control and is a part of the limbic system [5]. With the von Economo neurons being found in brain regions responsible for higher-order processes for intelligent organisms, VENs may be the key to understanding the true capabilities of the human brain.

Superagers and Memory

Von Economo neurons have been linked to Superagers’ memory. Superagers are peculiar individuals of age 80 or older whose episodic memory, the capacity to remember experienced events, is on par with that of cognitively average individuals in their 50s and 60s or younger [6]. Post-mortem studies of superagers have discovered that they typically lack the characteristic sign of aging in the brain: the shrinking of brain tissue [8].

However, what sets superagers apart from the majority of the population is their daily lifestyles. Cognitive neuroscientist Emily Rogalski from Northwestern University stated, “Superagers have unique personality profiles. They typically stand out for their resilience, optimism, and positive social relationships” [1]. The differences in their social relationships are what led to the discovery that superagers have more von Economo neurons in the fronto-insular cortex and anterior cingulate cortex. Rogalski also mentions that “superagers had four to five times more of those neurons than the typical octogenarian, an individual between the ages of 80 and 89. More even than the average young adult” [1]. As superagers are shown to have less brain shrinkage in the brain cortex, the outer layer of the brain where the fronto-insular cortex and anterior cingulate cortex are found, many von Economo neurons do not die or disable with age [6]. This key difference in von Economo neurons between superagers and the general population implies that these neurons have functions related to episodic memory.

Neuropsychiatric Disorders

At birth, a newborn only has 15% of the total von Economo neurons present in adulthood. Von Economo neurons are created until the child reaches the age of 4 [9]. Figure 2 details the number of VENs present in a human newborn compared to humans above age 4. VENs may be related to neuropsychiatric disorders that involve the fronto-insular cortex and anterior cingulate cortex, such as obsessive-compulsive disorder, psychopathy, and forms of dementia.

Another disorder VENs may play a role in is autism [9]. When comparing 9-year-old subjects
with and without autism, scientists found that the children with autism had VENs in a different orientation in the anterior cingulate cortex and the fronto-insular cortex. This difference in cellular architecture of the neural tissue is highly likely to have repercussions on various brain functions [9].

Furthermore, additional compelling evidence for the link between VENs and autism is provided by neuroimaging studies. When autistic subjects were placed in an experiment with non-autistic subjects where they had to determine the mental states of the people in photographs, feelings of empathy activated the fronto-insular cortex in non-autistic subjects, but not in autistic subjects [9]. This suggests that because of the differences in cellular makeup between autistic and non-autistic subjects, they respond differently to stimuli involving higher-order processes, such as empathy [9].

**Future Research Regarding Von Economo Neurons**

Von Economo neurons have been proven to have links to higher-order processes in humans. However, more research is needed to truly understand the complexities of VENs and how they interact with other brain centers.

Further research has to be conducted on the link between autism and the different cellular positions of VENs in the fronto insular cortex and the anterior cingulate cortex. Specifically, there is likely to be a pattern between the variation from the normal position of VENs compared to the position of VENs in the brains of those with autism.

In addition, VENs with one long basal dendrite have a very unique morphology compared to pyramidal cells with branching dendrites [2]. An interesting question for potential future research is whether the VEN’s dendritic morphology is altered due to autism. Would preventing the change in morphology prevent the other symptoms or the development of autism? Von Economo neurons may be key, in order to develop the technology notable in science fiction: enhanced human intelligence.

Von Economo neurons may have links to higher-order processes such as empathy, decision making, and memory, but more research is necessary in order to fully understand their role in the human brain.

References


Why We See Faces Everywhere: The Pareidolia Phenomenon

Patryk Wekwejt

Abstract

Pareidolia is a visual hallucination based on seeing recognizable patterns in objects and abstract installations [1]; a similar phenomenon is observed in auditory hallucinations. Most people have probably never heard of pareidolia, however nearly everyone has experienced it in some form. In our daily life, we are exposed to a lot of faces, so it is unlikely that we recognize all of them correctly. Our quick process of face perception makes us see faces in face-like objects. To achieve this effect, our brains need only two dots and a correctly arranged line. A simple example of ingenious use of face perception are the commonly used emoticons, which not only show faces but also represent feelings. There is also a wide spectrum of applications of the pareidolia phenomenon in medicine. The presence or absence of pareidolia in some cases may serve as an auxiliary diagnosis and it can also be a subject of research [2].

Pareidolia: A Psychological Phenomenon

As we know, the world that surrounds us consists of many shapes, figures, and polygons; one of them is the human face. Have you ever seen faces or other common shapes in clouds or treetops? If the answer is yes, you have in all probability experienced the phenomenon of pareidolia. Nevertheless, our minds are not the same, so some of us identify certain pareidolia hallucinations as meaningful while others see them as meaningless.

Studies show that we see faces in a slightly different way than other non-facial objects; our brains process a significant part of facial signals subcortically, non-intentionally, and irrespectively of visual attention. Our brain can process face stimuli independently of visual attention (likewise with pareidolia-causing shapes), in contrast to non-face stimuli. It is also worth mentioning that both real faces and pareidolia objects are mainly processed in the FFA (Fusiform Face Area), which is activated earlier during observation of facial structure than during observation.
of non-facial objects (∼130ms for real faces, ∼160 for pareidolia causing objects) [3]. This means that our brain does not need a reinterpretation process to recognize faces because the whole action happens almost simultaneously. Moreover, humans focus their awareness much more on anthropomorphically-shaped objects. An example from everyday life could be a situation when you are able to remember the face of a person you just met, but are unable to recall their name. This happens because the perception of a face is one of the most developed human skills and it evolved before the ability of speech recognition and usage [5].

The Influence of Various Factors of Pareidolia

The phenomenon of pareidolia was captured by a Swiss psychiatrist and psychoanalyst Hermann Rorschach. He made use of it in the Rorschach inkblot test, which is commonly used in psychology during diagnosis for symptoms of impulsiveness or proneness to violence. This test consists of ten tables with colored and not colored inkblots. Standardized norms allow psycho-diagnosis of patients through their responses. Interpretation and the results of the test depend on focusing on whole blots or just parts of them [6]. However, as the present study shows, scores may differ not only because of mental illnesses or a type of psychosis, rather they also depend on the environment in which the examined people live. Results (objects seen by patients in blots) differ for people from divergent backgrounds, different primary languages or levels of education [8].

A similar research difference is noted in pareidolia itself. According to the scientists from the University of Helsinki, people who profess faith are more likely to share acquiescence bias opinion (tendency to choose a positive answer; in this situation perceive faces in ambiguous images) and see faces in face-like objects more commonly than people who are atheists. Moreover, believers more often detect faces in no face-like areas, which means they are more susceptible to false alarms and have more extensive criteria in the perception of faces; they were more accurate in seeing faces in pictures with pareidolia-causing shapes [9].

Furthermore, the intensity of pareidolia does not only depend on what we believe in and who we are but also on diseases we have. There is a difference in seeing faces in face-like objects in people diagnosed with neurological diseases, like DLB (Dementia with Lewy Bodies) or PD (Parkinson’s Disease). Pareidolia could be a vicarious indicator of hallucinations seen by patients, which appears mainly in the form of faces and animals. Patients suffering from DLB demonstrated pareidolia more often than patients with PD, Alzheimer’s disease, or healthy adults. However, it is
difficult to elaborate if patients experienced pareidolia itself because in diseases like PD, hallucinations and delusions are common (mostly in cases with dementia) and even sometimes healthy individuals do not recognize pareidolia as pareidolia, due to its common presence in our lives [10].

Parts of the Brain Responsible for Pareidolia

The FFA (Fusiform Face Area) is the part of the brain where most of the face perception process takes place. It is located in the fusiform gyrus, in the inferior temporal cortex (the bottom part of the temporal lobe). Considering the brain lateralization, it is generally larger in the right hemisphere. Nevertheless, during observation of faces and pareidolia stimulating images, brain activation can also be observed in PFCX (Prefrontal Cortex), V1 and V2 areas (Visual Cortex) [11]. During the investigation of the brain and searching for a part responsible for processing face images using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), a difference between normal and abnormal patients' FFA activity could be seen. Although the decreased activity in FFA is discernible in individuals who have mental disorders like SAD (Schizoaffective disorder) or in those who abuse specific types of stimulants, the pareidolia and face recognition process is similarly noticeable as in healthy individuals [13].

In the previous study, researchers found that the pareidolia and the face perception process starts to develop in infants. Infants older than 6 months have a sound-mouth association; it was supported by the study in which infants were looking at the natural place of the mouth on four-blobs face during a sound presentation. It also showed that the intensity of pareidolia experience and ability to perceive faces in objects increases with age [14]. This implies that they recognize face layout while looking at the real face as well as in simplified face-like objects like specific paintings, abstract structures, or the facial schemes mentioned above.

Auditory Pareidolia

Our brain, trying to find a hidden message in illogical audio, produces random meanings and creates words or sentences. That’s why we can hear seemingly normal conversations instead of some computer-generated or even traffic sounds and misinterpret them as music or dialogue. The brain recognizes similarity in sounds we have heard in our lives mere seconds before and some random voices. Auditory pareidolia should not be confused with auditory hallucinations which differ in the cause of their creation. Auditory hallucinations are usually consequences of diseases such as Alzheimer’s disease and other types of dementia, schizophrenia, neurological conditions, cerebral
tumors or alcohol and drug consumption [15]. However, the cause of auditory pareidolia is a random stimulus, from which people build strings of words or letters and perceive them as meaningful. Generally, pareidolia is based on stimulus which exists in contrast to hallucinations that can occur even in perfect silence.

The genesis of auditory pareidolia could potentially be a part of the auditory pathways (which we can be distinguished into e.g. Brodmann areas 41 & 42, associative cortex), where our subconscious and other elements work [16]. Our sound reception of unconscious sound stimuli mainly depends on our past experiences (similarly to visual pareidolia), one of the factors of this being that we try to associate things we discover and come up against the first time with things we are close to.

Auditory pareidolia can have its basics not only in the physiology of the brain but also in the frequency of sound. This phenomenon is called the Doppler Effect, which refers to the differences in the frequency of the sound wave. During the approach of the sound source, it seems to be higher than when it is receding (of course, in both cases the distance from the sound source is identical) [17]. A similar effect could be noticed when the listener is moving relative to the source of the wave. This means that pareidolia can occur not only because of the neurophysiology of the brain but also because of the laws of physics.

Conclusion

Pareidolia, being a gripping phenomenon, which allows us to perceive some random objects and sounds as meaningful, could also be an auxiliary diagnosis for detecting brain diseases and abnormalities (as in the case with The Rorschach inkblot test). On the grounds of the presence and the intensification of the pareidolia phenomenon, mental disorders and diseases like PD or DLB can be diagnosed. However, we have to remember that the pareidolia in itself is not a sign of any mental disorder. The circumstances in which people prefer to look at anthropomorphic shapes have been used in marketing and product design, one of the simplest reasons being a greater, of course subconscious, demand for products. It is interesting to think about how something you perceive as significant could only be an intriguing cloud.

References


A Peculiar Disorder: Phantom Limb Syndrome
Divya Venkataraman

Abstract
It was the month of July 1886 when “The Case of George Dedlow” had been published. Due to unfortunate events in the Civil War, Dedlow had lost both his arms and legs. The ultimate phenomenon was when Dedlow complained of experiencing clenching and burning in the area where his limbs would have been. Dedlow recounts, “I had begun to suffer the most acute pain in my left hand, especially the little finger; and so perfect was the idea which was thus kept up of the real presence of these missing parts, that I found it hard at times to believe them absent.” Unfortunately, this syndrome was discovered by Ambroise Paré in 1552, through the study of the treatment of wounded soldiers (like Dedlow), and it did not gain recognition until Silas Weir Mitchell named the syndrome years later in 1871 [9]. He decided to name it ‘Phantom Limb Syndrome,’ due to the presence of the ‘ghost’ of a body part [6]. The peculiar Phantom Limb Syndrome, which affects 7 out of 10 people who undergo amputation, is when a patient feels like an amputated limb is still attached to the body. Severe cases of the Phantom Limb Syndrome cause chronic pain, which unfortunately drives some patients to commit suicide [7].

Causes and Risk Factors

Muscle movement is triggered by signals from the brain, especially the motor cortex and the cerebellum. However, whenever this relay network (brain, spinal cord, nerves: peripheral nerve, or joints) is damaged, the signals are unable to pass, and this prohibits muscle movement. While environmental conditions are more common causes of paralysis (such as accidents during war), genetic factors do influence this as well. In fact, birth defects, such as Spina Bifida, often cause paralysis in newborns. Additionally, gender or race does not affect paralysis nor Phantom Limb Syndrome in any way [2].

Although the exact causes of a paralyzed limb becoming a phantom limb are unclear, Dr. V.S. Ramachandran, a neurologist and professor at the University of California, San Diego, studying neurological mechanisms, explained this theory: After the limb has been amputated, since
the signals have nowhere else to go, the brain remaps the pathways, with the help of many proteins. The remapping is due to confusion in the brain and the spinal cord. These new pathways are then redirected towards another body part with another sensory circuit to transmit the signal. So, when this new body part is touched, it is almost as if the amputated limb was touched, due to the tangled wires. Since the brain doesn’t know how to act when this happens, the resulting response is pain [3]. Dr. Ramachandran proved this using a simple experiment. Blindfolded patients with Phantom Limb Syndrome were touched at various parts of their bodies, and they were asked to report whenever they felt pain in their phantom limb. Just like the hypothesis stated, when the face on the same side of the amputated limb was touched, patients reported pain in the phantom limb [7]. This articulates that the brain had remapped its nerves to react to a stimulus touching the face rather than the amputated limb.

Dr. Ramachandran also explained another possible cause of this syndrome: learned paralysis. This refers to patients who had to get their limb amputated due to prior paralysis. When the limb, before the amputation, was intact, but paralyzed, the brain tried to send commands to the limb, saying ‘move’. However, the only visual feedback the brain received said ‘no’. After multiple repetitions of the same thing, this new pattern gets wired into the brain, causing the learned paralysis. The brain learns this new Hebbian (associative) link, so much so that the command to move the limb causes the later amputated limb to create the sensation of the paralyzed limb [8].

There are two primary risk factors for Phantom Limb Syndrome. First, when a patient shows signs of pain before amputation, they are most likely to experience pain afterward as well. This can also be explained by learned paralysis. The second risk factor is residual limb pain. Usually, if the patient experiences pain in the remaining part of the amputated limb, they are at a higher risk of Phantom Limb Syndrome, since residual limb pain usually represents damaged nerve endings or abnormal growth [3].

Symptoms

The first type of symptom a patient may experience are non-painful sensations. This will typically cause the patient to experience movement, contact, temperature change, or itchiness in the once amputated, now phantom, limb [5]. The brain, brain lobes, and nervous system play huge roles.
in these symptoms since the brain becomes very puzzled when sending a nerve signal to the amputated limb to do a specific function. Why? Since the limb is no longer attached to the body, the lobe in charge of the function doesn’t respond. So, the only reaction the brain knows to give is pain [3].

However, patients more frequently experience the second type of symptom, painful sensations, named Phantom Limb Pain. This may cause patients to feel sharp and tingling pain in the area where the once amputated limb was. The pain tends to be excruciating, and patients have described the pain like tons of needles being pushed through the amputated area, shooting, stabbing, cramping, crushing, throbbing, or burning sensations [5]. This pain is primarily caused by the brain and spinal cord’s confusion after being forced to remap nerves that should have travelled to the amputated limb, to a new body part. While the pain for a few patients may come and go, many patients experience continuous pain, usually in the part of the limb that is the farthest from the body. For example, one would experience pain from the foot of their amputated leg, as shown in Figure 2 [3]. This excruciating pain that is experienced has horrible effects on a patient’s lifestyle, disabling them from doing many things that need limbs. As mentioned before, patients can even be driven to self-harm and suicide due to their inability to live with this unsourced pain.

**Diagnosis**

Although there is no official medical test to diagnose this peculiar syndrome, doctors can identify whether the patient has the syndrome based on their symptoms and prior circumstances. However, to do so, patients must precisely describe the pain they experience, to heighten the level of accuracy of the diagnosis, which could deeply affect the treatment they receive [7].

A few characteristics doctors use to help diagnose this syndrome are the symptoms experienced and the prior circumstances of the patient. The symptoms patients experience is the most straightforward way to characterize Phantom Limb Syndrome since doctors primarily look out for the symptoms described above. However, the patient’s condition before the amputation is a more complex contributor to diagnose this syndrome. Since, as described above, there are two potential causes of this syndrome, doctors can narrow their symptom search if they know the circumstance of the patient before the amputation [7]. Since not much is known about this syndrome, these are the main methods of diagnosing Phantom Limb Syndrome. Another possible complication to the diagnosis would be the varying levels of pain
experienced with this syndrome, since some patients experience intermittent pain, whereas others experience continuous pain.

Treatment and Ethical Views

There are many therapeutic treatments for Phantom Limb Syndrome. Some are pharma-therapeutic, including drugs such as gabapentin, tricyclic antidepressants, ketamine, amitriptyline, etc. Others are non-pharmacological, like repetitive transcranial magnetic stimulation (not an approved treatment yet, but it sends pulses to specific nerve clusters) [3], spinal cord stimulation, acupuncture (eases pain) [3], hypnosis, and more. However, although these treatments work, they may not necessarily be the most economically efficient or financially viable.[1].

Dr. Ramachandran has recently experimented with a new treatment, called Mirror Therapy. Although it is more recent than most of the treatments mentioned above, it has potential in the neuroscience and medical fields. Dr. Ramachandran first started brainstorming this idea after he realized that Phantom Limb Syndrome has more connections to the brain than previously thought. Based on the causes mentioned above, he realized that to effectively treat this syndrome, he must trick the brain into unlearning the association between pain and phantom limbs. Unlike the expensive treatments mentioned in the first paragraph, Dr. Ramachandran used a $5 mirror box. This box was set on a table that was parallel to the patient’s face. The patient struggling from chronic Phantom Limb Syndrome was instructed to place his amputated arm on the non-reflective side of the mirror, and his normal arm on the reflecting side of the mirror (as shown in Figure 3). Although, when looking at the reflective side of the mirror, one would only see the reflection of the normal arm, the patient believed that reflection to be the phantom arm and thought that their phantom arm had returned! Once this occurred, Dr. Ramachandran instructed the patient to move their normal arm. The patient then saw the mirror reflection of their normal hand, thought to be the phantom hand, moving. This command had been sent to the phantom arm, which then caused the visual illusion that the phantom limb is moving, obeying the brain’s command. This then tricks the brain into thinking that the phantom limb is not paralyzed anymore, which stops the brain’s confusion, causing no more pain signals to be sent. This may be hard to believe at first, but since patients typically don’t suffer from delusions, they do know that their phantom limb has actually not returned. Then why does it still work? Well, the visual illusion is still enough to allow them to trick their own brains into
subconsciously thinking that the phantom limb has returned, stopping the brain’s confusion, hence stopping the excruciating and suicide-driving pain [7].

Fortunately, there aren’t many ethical issues surrounding Phantom Limb Syndrome, however this can be attributed to the fact that very few people know that this syndrome even exists! However, there are a few issues surrounding this peculiar syndrome. Way back when, when Ambroise Paré first discovered this syndrome in 1552, doctors would not believe that this was true, and usually sent the patients to a psychiatry ward. Although many doctors and researchers now know better, much of the population who has heard of this syndrome and who aren’t educated about the science behind it, still believe this syndrome to be ‘crazy’ and ‘impossible’ [6]. This is why scientists such as Dr. Ramachandran are trying to educate the public on the Phantom Limb Syndrome, and how it is actually a serious and debilitating chronic.

Discussion

The most recent research surrounding Phantom Limb Syndrome has been Dr. Ramachandran’s breakthrough work with the mirror box, providing a feasible, efficient, and economically stable solution to patients who may suffer from this syndrome. Mirror therapy is an effective treatment for this unfortunate syndrome and is helping several patients even as you are reading this. The primary issue with mirror therapy (in 2016) was that, unlike other treatments mentioned, it had not undergone as much testing as needed to assess its accuracy, prohibiting it from becoming a first intention treatment for the syndrome [1]. However, as of this writing, more testing has been done. Since this new treatment is not only beneficial for patient health but also is helpful in financial aspects and monetary cost, there aren’t many societal or ethical issues about the treatment. Besides this new treatment, Dr. Ramachandran has also written various books, including The Tell-Tale Brain, which has gained exposure for this peculiar syndrome called Phantom Limb Syndrome, a disorder that was not very well known nor perceived in the past, but is slowly gaining proper recognition [7]. So, if we were to travel back in time to the civil war, when George Dedlow lost his limbs, we can hopefully help with this newly discovered mirror therapy, saving his, and many others’, lives.

References


Alzheimer’s Disease: The Reality of Finding a Cure

Maya Sharma

Abstract

Alzheimer’s disease (AD) is the sixth leading cause of death in the United States [1]. It impacts the older population, most particularly, women, and it is a brain disorder that progressively destroys memory and thinking skills, and eventually, hinders one’s ability to carry out the easiest tasks such as turning on a stove or driving a car. Even though AD was discovered more than a century ago, finding a cure has been elusive. AD is an incurable disease because of the lack of a deeper understanding about amyloid plaques and tau tangles that form in the brain, the late diagnosis of the disease, and the inability to replicate the disease on animals to further research.

Alzheimer’s Root Cause – Amyloid Plaques and Tau Tangles

Alzheimer’s is a disease occurring in more than 5.5 million Americans, most of whom are around 65 years or older [1]. AD is the most common source of dementia (loss of cognitive function such as thinking, reasoning, and remembering among older people) and was discovered by Dr. Alois Alzheimer in 1906. He had a female patient who had died of an unidentified mental illness, and after examining her brain tissue, he found many abnormal masses and tangled bunches of fibers which are now termed as amyloid plaques and tau tangles [1]. These amyloid plaques and tau tangles are the main features of AD today. In addition to these characteristics, there is also a loss of connections between nerve cells, or neurons, in the brain [1].

Neurons are specialized cells that process and send information with the help of electrical and chemical signals throughout the brain. In healthy people, neurons control all sensations, movements, thoughts, memories, and feelings. These nerve cells communicate with each other through electrical signals that travel down axons. This causes the release of chemicals across tiny gaps called a synapse, to neighboring neurons. AD breaks up these communications in neurons, consequently, leading to a loss of function and cell death [1].

Microglia and astrocytes are two variants of glial cells. In the case of a bacterial infection, glial cells can get rid of bacteria in the area surrounding neurons to keep them healthy. In a person with AD, toxic changes such as the accumulation of amyloid plaques and tau tangles, destroy this
healthy balance of microglia and astrocytes [2]. These changes in the brain can occur years, even decades, before the first signs of AD appear. As these accumulations increase, neurons are destroyed, and as a result, the brain shrinks and loses various functions. For example, the brain could lose glucose that is needed to power activity, or the vascular system may fail to deliver sufficient blood and nutrients, such as omega 3, to the brain [2].

Eventually, neurons lose their ability to communicate and so the brain shrinks, beginning in the hippocampus, which is crucial to learning and memory. Then, an AD patient may experience memory loss, impaired decision making, and sometimes even language problems. As the advancement in brain imaging occurs, we are able to expand our understanding of the disease and possible cures [2].

The brain is the most complex part of our body with over 100 billion neurons which are interconnected to form a network that allows for information to flow throughout our body, from thought processing to movement. In Alzheimer’s, the patient loses some of the functional capabilities of the cells and the breakdown starts to have an impact on the neural functions. Scientists think that the main reason why this is happening is due to the two main abnormal proteins – amyloid plaques and tau tangles that irreparably damage the nerve cells [3].

During the progression of AD, toxic changes occur in the patient's brain, including the aggregation of amyloid plaques and tau tangles. The proteins involved in these toxic changes are amyloid plaques, beta amyloids, and amyloid precursor proteins (APP). Amyloid plaques are protein parts that the body regularly produces. Beta amyloids are protein pieces cut from APP (in AD, APP is responsible for the production of beta amyloids).

The amyloid plaques are broken down and removed in healthy brains, however, in the brain of an AD patient, amyloid plaques clump together and become solid, insoluble accumulations between nerve cells. In the brain, the small strands can be easily dissolved in the fluid between cells. Sometimes, the enzyme that is used to cut the APP proteins is not always accurately cut, resulting in larger strands that are not able to dissolve in the fluid between nerve cells. The longer strands are “sticky” which allows them to start clumping into deposits called plaques. The presence of these plaques can trigger an immune response in the area resulting in neuron death. [3].

Neurofibrillary tangles are insoluble twisted fibers that are located in the brain’s cells. The tau tangles are made up of proteins called tau, that makes up part of a structure called a microtubule. Microtubules help transport nutrients or other necessary substances from one part of a nerve cell to
another. In a patient with AD, the twisted fibers create tau tangles when the tau proteins are misfolded in a very particular way. The tau forms a C-shape in the main part of the tangle where the loose ends stick out randomly. After one tangle has been created, it triggers a collection of more tau to make the tangle bigger. Scientists have not discovered why or what is responsible for shaping the tau proteins into these specific forms, but there is most likely an unidentified molecule involved. Amyloid plaques kill neurons by destroying connections between nerve cells. Tau tangles aggregate inside the neurons and intrude with cell machinery to create and recycle proteins which then kills the cell [3].

**Difficulty in Finding a Cure for Alzheimer's**

Billions of dollars have been spent on finding a cure for AD, but researchers are nowhere near understanding the disease in its entirety [4]. Unfortunately, the question of reducing or being able to dissolve amyloid plaques has not been answered despite being heavily focused on for the past few years in drug development. After failures in numerous clinical trials, doctors and researchers have begun to wonder if clearing amyloid plaques is sufficient to cure AD.

Although a significant amount of research has gone into finding a cure for AD, the research process has been highly inefficient. For example, even though more than 400 trials have been done on people with potential treatments for AD, no drugs have been put on the market [7].

Ever since Alois Alzheimer discovered the disease, there has not been any grand theory that really explains how Alzheimer’s starts to impact the human brain. In fact, a Texas businessman who lost family members announced a $4 million prize for researchers who can help explain the disease. James Truchard, the former CEO of National Instruments, said, “The pieces of this puzzle are out there. ApoE4, beta-amyloid, tau, microbes, inflammation, metabolism, FOXP3, and APP are only some of the genes, peptides, and biological processes that have been identified as contributing to Alzheimer’s, but they have not been synthesized into a ‘grand unified theory’ of Alzheimer’s that might lead to a treatment or cure. I’m hoping there’s some genius out there who will put them together” [8].

Researchers have started to take a more holistic view to address the quest of finding a cure for AD. The sections below discuss why it has been so difficult to find a durable AD cure.
Researchers have been working to figure out an approach to clear the accumulation of toxic proteins that form in the brain of patients with AD. The brain's circulation is tightly controlled, unlike circulation in other parts of the body, which means that it is able to keep out harmful substances, such as damaging chemicals or infections. This also means that the brain does not allow medications to enter its domain, so, scientists are not able to get rid of excess toxins like amyloid plaques and tau tangles since medications cannot cross the blood brain barrier, thus unable to reach the brain [9]. The pharmaceutical company, Biogen in Cambridge, Massachusetts has been doing trials with a drug called aducanumab that has been halted after ongoing trials that were not yielding promising results. Derek Lowe, an organic chemist says, “the situation [of amyloid plaques and tau protein tangles] is clearly more complicated than people have hoped, because otherwise, all the attempts to address amyloid...would have yielded some tiny bit of clinical benefit” [10]. Another researcher, Richard Hodes, director of the National Institute on Aging said, “it’s critical as we await more information about [the aducanumab] study...that we continue to actively and broadly pursue multiple candidate targets” [10].

From the analysis of these two researchers, it is very clear that the research community focusing on AD do not have enough knowledge about how drugs can be used to reverse the toxic build-up in the brain. In order to create a cure for a disease, it is important to understand every aspect of it and create a drug that can “counter” the effects that the disease has on the human body. However, because researchers have not been able to discover a way to even get medicine into the brain, they do not understand all the factors that go into play when amyloid plaques and tau tangles collect inside and on nerve cells. After clinical trial failures, researchers are still unsure if looking for a way to stop the toxic build-up is the right move to finding a cure for AD.

Late Diagnosis Prevents Cure

Scientists have learned that the accumulation of amyloid plaques and neurofibrillary tangles attacks the brain long before a patient manifests memory loss or cognitive decline due to the improvement in brain scanning technology [11]. This is a serious problem because scientists can only test drugs on AD patient’s once they showcase these symptoms, but by the time that happens, they do not have much time to live. This is one of the main reasons for constant failure in clinical trials on AD, simply because the drugs are given too late.

In fact, Dr. John C. Morris, an Alzheimer's specialist at Washington University in St. Louis, says, “there’s a lot of brain cell damage [by the time the patient is given drugs] and we’re trying to treat a very damaged brain” [11]. This means that there is no point in inducing a patient with certain drugs when too much of the brain is already damaged. If the drugs are given earlier in the progression of the disease, tailored toward certain biomarkers in the brain, then treatment or possibly prevention, would have a higher rate of success. Researchers are doing this by, “trying to go earlier and earlier in the course of the disease...by locating how people move through these stages and what indications there are of each stage,” says Neil Buckholtz, chief of the Dementias and Aging Branch at the National Institute on Aging [11].
Many research projects are involved in doing just that. American and Colombian scientists are working together to plan to test treatments on Colombians that are destined to get AD, but have not showcased their symptoms yet, in order to see if dementia can be prevented or remarkably delayed. Although the diagnosis of the disease happens very late in its progression, significant work has gone into testing certain drugs on people that are most likely going to develop AD, through genetic mutations that can guarantee development of dementia, figuring out how people progress through the stages of the disease and what those stages are, and more [11].

**Alzheimer’s is Hard to Replicate in Animals**

Another important factor that plays into why researchers have not found a cure for the irreversible disease is that it is not easily replicable in animals. Drug testing on animals has been a reliable technique for the pharmaceutical industry to bring drugs quickly to the market. Researchers have been attempting to manipulate Alzheimer’s on animals by inducing symptoms that mimic dementia in humans so that they can test drugs on them before testing on people, but it has proven to be very difficult [11]. However, Matthew Campbell, a geneticist at Trinity College Dublin has noticed that, “while mouse models have provided astounding new insights into disease mechanisms, they don’t reflect the entire biology of the disease” [7].

Mouse models that can better reflect a more common and sporadic form of AD is something that researchers are now looking into. Researchers are very aware that certain areas of the disease, which are mimicked in mice, drift significantly from AD in humans. For example, one of the mouse models used to study AD involves overexpressing certain proteins that have mutations which result in a bigger aggregation of amyloid beta. These proteins include APP and PSEN1, which is a type of enzyme called gamma secretase that is required in APP processing. Even though this approach is used to understand amyloid plaques better, it is not very efficient since according to Takaomi Saido, a neuroscientist at the RIKEN Center for Brain Science in Japan, “humans do not overexpress APP or PSEN1” [7]. Thus, we need more knowledge and better data to replicate the disease in various animal species.

**Conclusion**

As previously discussed, it has been challenging to find a promising strand of research that might lead to an AD cure. Some of the research and lab work that is currently going on in different institutes includes working with amyloid plaques and preventing tau tangles and reducing inflammation. Researchers are producing new drugs to stop beta amyloids from clumping and encourage the immune system to keep harmful proteins away from the brain as well as figuring out how to fix the brain cell inflammation that occurs in AD [12].

Creating new drugs and medications to cure AD is a very slow and difficult task. To help speed up the discovery process, an association of multiple pharmaceutical companies, nonprofit foundations, and government guides, have partnered to create the Coalition Against Major Diseases (CAMD), where data from different AD clinical trials can be shared [13].
In addition to the partnership between different associations, there is a lack of funding and volunteers for clinical trials. According to James Pickett, the head of research at Alzheimer’s Society in the UK says, “dementia is the biggest health and social care challenge of our generation, but research into the condition has been hugely underfunded. This lack of funding has hampered progress and also restricted the number of scientists and clinicians working in the dementia field” [14]. Considering that we live in an app-heavy world, perhaps more cognitive, and neurological tests can take place to develop a more robust dataset and a volunteer network of millions of users that might lead to some early detection techniques that researchers have not been able to hone in on. By refining our collaborative approaches to researching an AD cure, the probability of success will improve and provide a source of hope for millions of patients and their families who go through this incurable disease.

References


Huntington’s Disease: An Overview

Jason Luo

Introduction
It is no doubt that neurological disorders and conditions are extremely lethal as they can attack one of the most vital organs in the body: the brain. Our brains are responsible for our daily functions such as regulating our coordination, encoding information, and storing short/long term memory through our neurons and brain cells. Huntington’s disease is a genetic and neurological disease that causes the death of nerve cells in the brain. This article will look at the effects and symptoms of Huntington’s disease as well as how it is diagnosed and treated in infected patients.

What is Huntington’s Disease?

Huntington’s disease is an autosomal dominant brain disease that results from an expansion mutation in the HTT gene on chromosome 4 [1]. The wild-type HTT gene is responsible for synthesizing a protein called huntingtin that plays a role in chemical signaling, transporting materials, and the prevention of apoptosis. Huntingtin, while present all over the body, is most abundant in the brain and is related to the proper function of nerve and brain cells [1]. The mutation in the HTT gene causes a DNA segment of the gene called the CAG (cytosine, adenine, guanine) trinucleotide to appear more than normal. Normally, the HTT gene has 10-35 CAG trinucleotides but the resulting mutation results in the CAG trinucleotide appearing 36-120 times [1]. Typically Huntington’s disease develops in patients between the ages 30-50 but could develop as early as 2 years old to as late as 80 years old[2].

Effects and Symptoms

The mutant HTT gene causes the synthesis of an abnormally long huntingtin protein that contains increased numbers of polyglutamate (polyQ) tracts on exon 1[3]. The increased amounts of polyQ tracts have been shown to lead to excessive amounts of the neurotransmitter glutamate, which acts as an excitotoxin, causing excessive firing and activation of the neurons. It is supposedly responsible for the symptoms in Huntington’s, although the specifics of this are not fully understood yet [4]. Many studies performed on rats show that excessive amounts of glutamate have caused them to exhibit symptoms of Huntington’s [4].
Research done on mutant huntingtin has shown that it can cause various disruptions in gene expression that are necessary for a nerve cell’s survival. For instance, mutant huntingtin has been shown to decrease the expression of GLT-1, a glutamate transporter which when expressed in normal amounts is responsible for uptaking and clearing the amount of glutamate in the synapse [5].

Without GLT-1, glutamate will accumulate in the synapse without any way to remove it. This accumulation can be damaging as extremely high concentrations of glutamate mean that the postsynaptic neuron will almost always have at least one glutamate ligand bound to its receptor. This can cause the neuron to become overexcited and fire absurdly, eventually leading to cell death [6]. The mutant huntingtin has also been shown to cause an imbalance in the amount of synaptic and extrasynaptic NMDA receptors (NMDAR), which allow the binding of glutamate as a ligand in order to trigger cellular responses. Synaptic NMDAR is a pro-survival receptor that activates survival genes in the neuron when glutamate binds to it, whereas extrasynaptic NMDAR activates genes that induce apoptosis when glutamate binds to it [7]. As a result, the increased amounts of glutamate and overexpression of extrasynaptic NMDAR results in accelerated nerve cell death.

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Figure 1. The diagram displays the cell signaling pathway of presynaptic and postsynaptic neurons, one wild-type and one Huntington’s. The Huntington’s (HD)-affected nerve cell has increased amounts of extrasynaptic NMDAR, which when coming in contact with glutamate, inhibits the expression of ERK and causes cell death [5]. Lack of GLT-1 in the HD nerve cell also limits the amount of glutamate clearance in the synapse [5].
The resulting loss of neurons can cause a wide range of symptoms. This can include developing movement disorders ranging from being as mild as having difficulty speaking, to more severe disorders such as chorea, the unpredictable and irregular movement of certain body parts like the arms and legs [8]. Death in the nerve cells has also led to many cognitive disorders such as lack of awareness, difficulty focusing on certain tasks/learning new information, and random outbursts of anger and control of emotion [8]. Patients with Huntington’s have also shown signs of sadness, depression, and even suicide due to the sudden changes in the brain [8]. The area in the brain where the most nerve cell death occurs is in the basal ganglia, which is responsible for regulating both motor movements and emotions and explains why most of the symptoms that occur are kinesiological or cognitive [9].

**Diagnosis**

Huntington’s shows a wide range of symptoms so there are many ways to diagnose a person who may be suspected of having the disease. A neurologist may interview the patient and ask them about any previous symptoms as well as their medical history. They can then perform various neurological and physical tests such as reflex, movement, hearing, and walking tests to evaluate certain motor and neurological functions and find any abnormalities in them [9]. Genetic tests may also be used since Huntington’s is a heritable disorder and has an equal chance of affecting men and women. Blood samples may be taken from the patient and then be examined to determine the number of CAG repeats in a person’s HTT gene [9]. Finally, brain imaging may be used to examine the shape and condition of a patient’s brain. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) are usually used as they give the most accurate picture of what a patient’s brain looks like [9]. Those with Huntington’s can expect to see shrinkages in areas of the brain such as the striatum of the basal ganglia. However, these results do not fully conclude a patient has Huntington’s as these symptoms can be seen in other disorders as well [9].

**Treatments**

As of now, there is no definitive cure for Huntington’s disease, and the treatment options currently available only lessen the existing symptoms. Such options include using drugs such as Xenazine and Klonopin to suppress the jerky and sudden movements caused by chorea [10]. While these drugs sound promising, they do come with their fair share of side effects such as worsening the existing symptoms of Huntington’s like depression [10]. Antipsychotic and antidepressants are also another form of treatment but they too can cause side effects such as dry mouth and can even worsen muscle rigidity and impair movement [10]. One a brighter note, speech therapy, psychotherapy, and physical therapy can help cope with the most common symptoms of Huntington’s such as trouble swallowing/speaking, thoughts of suicide, and trouble walking [10]. In addition, research being done now on Huntington’s revolves around blocking the activity of NMDAR with NMDAR antagonist drugs like memantine [11]. In the lab, scientists were able to use low doses of memantine in mice with Huntington-like symptoms and it has been shown to reduce downstream cell death and improve the motor movement of the mice [11]. Gene therapy is also being
researched, particularly antisense oligonucleotide therapy. This type of treatment involves synthetic DNA and RNA strands called antisense oligonucleotides that bind to the mutant HTT gene, acting as a repressor similar to how microRNA regulates the expression of post-transcriptional mRNA [12]. The binding would limit the ability of the gene to synthesize the toxic protein and thus limit the symptoms of the disease.

Final Words

Huntington’s disease has affected thousands of people in the US, killing those who cannot receive treatment and permanently handicapping those who manage to survive. Hopefully, gene therapy and medication can be administered in the near future and create a more hopeful future for Huntington patients around the world.

References


Schizophrenia and the Loss of Brain Matter
Olakunsi Peters

Abstract

Once someone is diagnosed with schizophrenia, it can be difficult for that person to navigate back into the life they had before being diagnosed. Schizophrenia can be different for everyone. Some may experience delusions and hallucinations, while others may experience various voices in their head. This is why researchers are working tirelessly to find a cure that can cater to many schizophrenics. From consistent symptoms to novel clinical trials, this paper will explore an overview of what goes on in the brain of a schizophrenic.

Symptoms

Schizophrenia is a disabling mental disorder characterized by delusions, disturbed perceptions, and inappropriate behaviors. People with schizophrenia may seem like “they have lost touch with reality.” For males, symptoms usually start in their early 20s, whilst for females, symptoms usually start in the late 20s. Schizophrenics suffer from both ‘negative’ and ‘positive’ symptoms – with the psychotic behaviors that are not seen in ‘healthy’ people considered as positive. Hallucinations, delusions, thought and movement disorders are all positive symptoms [2]. Negative symptoms include “inexpressive faces, blank looks, monotone and monosyllabic speech, few gestures, seeming lack of interest in the world and other people, [and] inability to feel pleasure or act spontaneously” [3]. Schizophrenics may not even find pleasure in their daily hobbies. Some patients may experience severe or subtle cognitive symptoms. Sometimes, their
working memory may be impaired. At other times, they may be inattentive [2].

Positive symptoms usually indicate whether or not someone has schizophrenia; acute treatments pinpoint these symptoms. Even though negative symptoms may occur early in this illness, they can be seen in the later stages. Those who have both types of symptoms respond positively to acute and aggressive treatments [2].

**Decreases in White and Grey Matter**

MRI’s and CT’s allow physicians to see the “structural and functional changes in the cortex” of schizophrenia patients. Functional imaging techniques also showcase abnormal activity during decision making and even short-term memory in schizophrenics [4].

MRI studies of schizophrenia display a decrease in grey matter in the superior and medial temporal lobe and the prefrontal lobe. All of these regions of the brain specialize in episodic memory, short-term memory, auditory processing, and decision making. The loss of grey matter indicates a reduction of synapses and dendrites [4]. A study conducted by the Johns Hopkins School of Medicine shows that grey matter loss happens early in the life of an adolescent who has schizophrenia (Figure 2). Deficits begin in the parietal region. Over the course of five years, the damage moved to the temporal lobes (specifically, the sensorimotor, dorsolateral prefrontal cortices, and frontal eye fields) [5]. These are the reasons why schizophrenics have psychotic symptoms [4].

This mental illness also causes disrupted neural connectivity [4]. White matter is made out of axons. Each neuron in the brain has a long axon that comes off of the cell body. Electrical signals from the cell body travel along the axon to other neurons [6]. Neuroimaging techniques have allowed scientists to see white matter reduction in both the first episode and chronic patients. The myelin sheath covers neural fibers and ensures that connections between the brain and body are efficient. From late adolescence to early adulthood, more myelin surrounds the neural fibers (myelination). This is also when psychosis starts to occur in schizophrenics. Scientists have theorized that a decrease in white matter in schizophrenics is related to a disruption in the myelin sheath [4].
MRIs have made it possible to see a reduction in grey matter in schizophrenia patients, but it is difficult to see what happens with the white matter. As a result, there are not many studies that have tried to find white matter differences between people with and without schizophrenia. Wible and coworkers (authors of “Prefrontal cortex and schizophrenia: a quantitative magnetic resonance imaging study”) [7] found associations between white matter and the temporal lobe (specifically, the superior temporal gyrus and amygda-hippocampal complex). Also, Breier and coworkers (authors of “Brain morphology and schizophrenia: a magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures”) [8] saw a reduction of white matter in the amygda and hippocampal complex [9].

Cognitive-Behavioral Therapy

Those with schizophrenia usually have lifelong treatment because there isn’t a cure. Chronic cases usually require hospitalization [10]. Cognitive-behavioral therapy (CBT) usually lasts an hour for 12 to 16 weeks. This therapy helps a schizophrenic think about their positive and negative symptoms differently. A therapist must find various ways to change any “negative thoughts” or delusions schizophrenics may have about themselves or the world around them [11].

According to Ann K. Morrison, MD in psychiatry, non-pharmacological therapy should be taken alongside medication, even though some schizophrenic symptoms resist pharmacological treatments [12]. An example of CBT is cognitive restructuring. In cognitive restructuring, the patient has to figure out various ways to show how some of their beliefs are unreal. As a result of having cognitive restructuring, many schizophrenics realize that they tend to have delusions from time to time. Over time, more positive thoughts will overcome negative thoughts. CBT can also improve a patient’s conversational skills so that they can work on previous relationships and form new ones [13].

Yoga Therapy

People with schizophrenia can also use yoga therapy with their medication to reduce symptoms. Yoga tends to help positive symptoms, negative symptoms, and weight gain. In contrast, weight gain, “endocrinological and menstrual dysfunction,” can be a result of antipsychotics [13].

A study conducted by N Gangadhar Bangalore and Shivarama Varambally [14] shows how effective yoga therapy is on patients. In this study, there were two groups of patients who were given antipsychotics. For one month (“12 sessions”), one group did yoga exercises while another group did physical exercises. In the end, the researchers saw a significant improvement in the yoga group as they had “better negative symptom scores than the physical exercise group.” It is reasonable to infer that yoga therapy worked because of oxytocin [14]. In another study done by David Feifel, patients who took oxytocin had less severe negative and positive symptoms [13].

Antipsychotics
First-generation antipsychotics (FGAs) or typical antipsychotics were created in the 1950s and second-generation antipsychotics (SGAs) or atypical antipsychotics were created in the 1980s. FGAs are serotonin-dopamine antagonists (a drug that blocks dopamine from binding to the receptor), while SGAs are dopamine partial agonists (a drug that activates the dopamine biological response) [13]. FGAs such as chlorpromazine usually bring along “metabolic adverse effects.” FGAs are best in decreasing many of the positive symptoms like hallucinations and hostility. SGAs such as Clozapine usually have “extrapyramidal side effects” (EPS). Clozapine is used after a patient does not show improvement with FGAs. This antipsychotic can also cause cardiac complications [14].

A trial was done by Afaque H Khan and Samina Zaidi, which showed improvements in negative symptoms. So far, Clozapine has been proven to be the best antipsychotics for schizophrenics who have persistent negative symptoms. Two of the patients showed improvements in “psychotic and negative symptoms including insight and judgement improvement in disorganization.” Two other patients “demonstrated robust response with significant improvement in negative symptoms including insight, judgment, affect, avolition, and disorganization and also an improvement in psychotic symptoms” [15].

Conclusion and Novel Treatments

Scientists have not yet found a cure for schizophrenia. It is unfortunate that in this year alone, there were 1.5 million around the world who were diagnosed with schizophrenia. Many children and teenagers will not know that they could potentially develop schizophrenic symptoms. Currently, researchers do not know how schizophrenia starts. However, they do know that schizophrenics produce too much dopamine, which leads to hallucinations and delusions. FGAs and SGAs do not help “cognitive impairments, lack of motivation, dulled emotion, and social withdrawal” [16].

Sunovion Pharmaceutical Inc. created a new drug to treat symptoms of schizophrenia, such as psychosis. After completing a clinical trial with 245 people, researchers found that SEP-363856 targets more symptoms and does not have as many adverse side effects. SEP-363856 affects receptors that allow for “dopamine signaling” [17]. These researchers created drug screenings with PsychoGenics Inc. Using artificial intelligence, they were able to see what would happen to mice as they came into contact with SEP-363856. Once the researchers found a drug that mimicked the effects produced by D2-targeting drugs, they were able to continue with testing. Interestingly enough, the researchers saw that SEP-363856 targeted TAAR1 and 5-HT1A instead of D2 receptors. Sunovion Pharmaceutical Inc. is still in the process of finalizing mechanisms, but SEP-363856 has opened new doors of possibilities [15].

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Tic Douloureux: An Overview
Aviral Batra

Abstract
Tic douloureux, or as it is more commonly known, trigeminal neuralgia (TN), is a chronic pain condition that affects the face resulting from a problem with the fifth cranial nerve, or the trigeminal nerve. It is characterised by sharp stabbing pains that can occur several times throughout the day. The name ‘tic douloureux’ or ‘painful tic’ comes from the facial expressions that patients make when wincing from the pain. The collateral effects of pain have led TN to gain names such as the ‘suicide disease.’ There are various options for treatment including pain medications and different surgeries to fix what is irritating the nerve or to damage the fibres that are transmitting pain. New drugs are also being designed to target the specific fibres causing pain.

A Very Brief History

The name Trigeminal Neuralgia is divided into two parts - ‘trigeminal,’ which indicates the nerve being affected, and ‘neuralgia’ which means a severe pain caused by the irritation of a nerve. Although this name is widely accepted today, the disease was once ‘tic douloureux,’ coined by the French doctor Nicolas André. ‘Tic douloureux’ in French or ‘painful tic’ is a reference to the wincing or facial tics that patients display as a result of the severity of the pain. Though the tics are not present in all patients, the name is still used [2]. Other names include prosopalgia (neuralgia affecting the face) and Fothergill’s disease, the latter signifying the first full account of the disease given by John Fothergill in 1773 [2]. However, descriptions of the
symptoms can be inferred from the writings of Galen, the famous ancient physician born around 80 AD and of Avicenna, a significant Persian physician and polymath during the 11th century [2].

An Introduction to the Trigeminal Nerve

The trigeminal nerve is the fifth cranial nerve and it originates from a section of the brainstem known as the pons. It has 3 divisions: the ophthalmic division, giving sensation to the upper third of the face, the maxillary division, which provides sensation for the middle third of the face, and the mandibular division, which relays sensory information from the lower third of the face to the brain. The mandibular division also innervates the muscles required for mastication (chewing) [3]. It is usually the maxillary division that is involved in TN, however, the mandibular and ophthalmic divisions can be implicated as well. disturbances in the sensory divisions of these nerves cause the symptoms of intense pain in TN [4].

Pathology and Causes

There are two ways in which TN can manifest itself: classic and symptomatic. The classic form is usually idiopathic (it arises spontaneously) and no cause can be identified other than a normal blood vessel compressing or coming into contact with the trigeminal nerve [6]. Symptomatic forms are caused by another underlying cause that irritates the nerve. This could range from tumours to aneurysms (enlarged portions of arteries due to wall weakness) that could compress the nerve [6].

Another less prevalent way in which TN can occur is if a person has multiple sclerosis (MS). Oligodendrocytes are cells in the central nervous system (CNS) - primarily consisting of the brain and spinal cord - that form myelin sheaths that wrap around neurons. Myelin sheaths are fatty and act as insulating deposits on neurons that speed up the transmission of nerve impulses necessary to maintain neurological function in areas of the CNS. In MS, immune cells from the blood can enter the CNS and cause inflammation, attacking the myelin of these oligodendrocytes, leading to lesions (areas of damaged tissue). When the damaged myelin is replaced by scar tissue, this is called a plaque, which is harder than the myelin that was present before. This is why the disease has the word ‘sclerosis’ in the name, as ‘sclerosis’ means hardening [7]. When this damage occurs in areas near the pons and on the trigeminal nerve, it can give rise to symptoms of TN. TN caused by MS shows similar relative statistics to the idiopathic kind – they are both more prevalent in women and more often present on the right side of the face than the left [8].

Symptoms and Diagnosis

The main identifying characteristic of TN is brief, intense, stabbing pains on the face that are paroxysmal (sudden, lasting for a few seconds and a few minutes at most). They are usually unilateral (on one side of the face) and can very rarely be bilateral (on both sides of the face) but even then the pain does not often occur simultaneously on both sides. If the pain is bilateral, there could be some underlying disease such as MS, which could irritate the nerve on both sides [9].
Furthermore, although the pain can occur spontaneously, there are very few, if any, cases of TN that do not have stimulus-evoked pain as well; most cases have a combination of both [9]. Stimuli in the sensory areas which the trigeminal innervates, such as even a light touch, can cause the pain to occur.

The diagnostic criteria for TN revolve around these symptoms and combining them with the use of scans allow doctors to discern what is causing the pain. Doctors do a neurological differential diagnosis: they match the symptoms up with the various disorders, which could be causing them, and then using various tests, clinical experience, and patient history, they can eliminate the most unlikely causes [6]. In the case of TN, the main criterion is paroxysmal and sharp pain [6]. Then the doctors differentiate between symptomatic and classic. The patient history and details of the patient are incredibly useful, for example, patients under 40 are generally unlikely to have the classic form of TN and the patient’s age can be used to discern the likelihood of this [6]. Scans are done using magnetic resonance imaging (MRI) or a computed tomography (CT) scan, which can give vivid images of the brain and can identify if there is a tumour, or some scans can identify if there is a blood vessel compressing the nerve. Throughout this process, the various potential causative diseases can be ruled out, for example, cluster headaches could cause pain, but if they last a longer period of time and are in non-trigeminal areas, then they can be ruled out as the cause [6]. This may seem simplistic and obvious, however, when the symptoms are less conspicuous, differential diagnosis becomes all the more important. For example, more subtly, in TN, the physical examination is usually normal so an abnormal physical exam relating to the pain can suggest another cause [6]. After considering all of these factors, a physician can come to a final diagnosis.

The pain is also responsible for some psychological symptoms of the disease; TN has been referred to as the ‘suicide disease’ [10]. The excruciating pain caused by TN can be debilitating and its severity can cause psychological distress. Some studies have drawn an association between TN and psychiatric disorders, for example, a study by Wu et al., doctors and information specialists in Taiwan, has shown that within the patients they observed, there was a higher risk of developing anxiety and depressive disorders if the patients had TN [11].

Treatment

In the past, a lot of experimentation was done to treat this sort of facial pain. Research and discoveries have assisted the development of treatment alongside experimentation. After 1820, the trigeminal nerve was discriminated from the facial nerve and then surgery began to play a larger role in treatment. Surgeons have tried many different techniques, including neurotomy (cutting the nerve) and neurectomy (removing all or part of the nerve) which were often unsuccessful at the time [2]. Since then, the evolution of surgery and medicine has increased the success rate and allowed TN to be treated and controlled.

The first line of treatment is the use of medication. Carbamazepine, an anticonvulsant (reduces the instances of involuntary movement) and analgesic (helps to relieve pain) drug, is initially administered to control the symptoms of TN [1]. Other anticonvulsants and analgesics can
be prescribed if the patient is allergic or the medication does not work. The psychological symptoms that come alongside the disorder such as depression can be treated by administering antidepressants [12].

If medication has little effect, then surgical treatment can be considered to reduce the passage of pain signals through the nerve. In the classical form, when it is a vessel that is compressing the nerve, there is a type of surgery known as microvascular decompression (MVD) which can be done laparoscopically (through a small incision with small camera and tools inserted through) [14] (see left). The offending vessel is approached and a sponge is placed between the trigeminal nerve and the vessel to create relief from pain [14]. Another effective surgery for the disease is stereotactic (precision positioning of surgical equipment) radiosurgery. This involves using a so-called knife ‘made out of’ radiation to target fibres in the trigeminal nerve and damaging them in order to halt or reduce transmission of pain signals [14]. Radiation is focused onto one point by using around 200 beams from different directions. Individually, the beams have little impact on the tissue they pass through, however, the point where they intersect receives a very large quantity of radiation and can be damaged in a very targeted way [15] (see below). Unlike microvascular decompression, it does not tackle the problem as its root cause, but instead, attempts to prevent the pain signals traveling at all. This is a non-invasive surgery so it means the patient does not have to be under general anaesthesia (to make them unconscious during surgery) and therefore is of benefit for those unwilling to go under general anaesthesia or are medically unable to do so [14]. Other procedures that aim to treat TN by destroying fibres in the trigeminal nerve are called

Figure 2. Microvascular decompression depiction [13]

Figure 3. Simple diagram of how a gamma knife works [16]
percutaneous (through the skin) stereotactic destructive procedures. An example of this is when an electrode is passed through the skin to a portion of the trigeminal nerve. When a heating current is passed through the electrode, it can destroy some nerve fibres in the trigeminal nerve. This can cause a degree of facial numbness but this is important for recovery from the painful symptoms of the condition [14].

**Future Prospects**

One of the main avenues of future treatment for TN is designing specific drugs to target the pain specifically and reduce it substantially. Current drugs are useful in controlling pain but not getting rid of it completely. A new drug known as BIIB074 is in the trial for TN and other chronic pain conditions[17]. In pain-causing conditions such as TN, it is the opening of sodium channels that allows for the transmission of pain signals. There is especially a large number of a type called sodium channel 1.7 in pain-causing nerves. This new drug acts in a way that blocks these channels. The drug also increases the strength of blocking the more active the channel gets. This allows greater levels of blocking where there is more transmission; where the pain signals are being sent. It targets the area of pain and mitigates the side effects that come with some other drugs that act on sodium channels no matter their activity levels [17].

**Conclusion**

TN is a unique, severe pain condition that affects the face. It is a result of irritation of the trigeminal nerve which is one of the main nerves that originate in the brain - specifically the brain stem. In TN, it is interesting that even though the pain may be perceived as physical, there is a huge psychological component to the disease - supporting that there is a link between psychological and physical pain in the body. It is hard to diagnose and the characteristic pain could be due to a whole host of different factors thus TN is by no means the most likely. However, with specialist diagnosis, it can be identified and tackled. Techniques to treat TN have developed over time and mitigated the consequences of early forms of treatment, for example, complete facial numbness caused by neurotomy. Now with modern drugs and surgeries, doctors can target treatments to the specific fibres that cause pain.

**References**


Fusogens: Glycoproteins That Mitigate Fatal Neurological Conditions

Charlene Cai

Introduction

Currently, there are no official treatments for reversing spinal cord damage [1]. There is no cure for the more than 5 million senior citizens who have Alzheimer’s disease [2]. In fact, one of medicine’s greatest adversities is the restoration of function after nerve injury or degeneration [1]. Nevertheless, research is still being conducted and a lead has been found regarding possible treatments for neurological injuries, diseases, and other conditions: fusogens. Fusogens are glycoproteins which station themselves inside or on cell membranes and interact with other cell membranes to overcome, control, and regulate the forces that inhibit spontaneous membrane fusion. Besides neurological applications, fusogens have also been found in promoting muscle cell fusion, sperm-egg fusion, macrophage fusion, cancer metastasis, epithelial cell fusion for eye lens formation, and other implementations [3].

However, focusing on the neurological aspect, a wide variety of fusogen classes allow for multiple medical issues to be mitigated. With further experimentation, the modern healthcare field may experience a variety of new treatments for “impossible” situations thanks to fusogens.

Epithelial Fusion Failure-1 and Anchor Cell Fusion Failure-1 for Axonal Fusion

Axonal fusion mechanisms are crucial to any regenerative goal in the body; they represent means of functional restoration after neuronal injury. Two studies performed in 2017 by Basu et al. and Abay et al. indicate that axonal fusion in Caenorhabditis elegans, a species of roundworm, repaired severed mechanosensory neurons, restoring full function. Axonal fusion requires the damaged axon to undergo regrowth, reconnection, and fusion processes. To regrow, the proximal axon must make its way towards the distal fragment and then make contact to initiate reconnection. This occurs when phosphatidylserine (PS) attaches itself to the exterior membrane of the severed axonal segments to function as a rescue signal after neuronal injury. Lipid binding proteins TTR-52 and NRF-5 bind with the exposed PS. The two parts of the axon must merge to create a continuous axonal membrane in order to fuse. CED-6 and PSR-1 molecules are involved with reconnection, but fusogens Epithelial Fusion Failure-1 (EFF-1) and Anchor Cell Fusion Failure-1 (AFF-1) regulate the majority of axonal fusion in C. elegans. EFF-1 proteins are inserted into both ends of the severed...
axon, so that the fusogen can form bonds across the gap. The proteins then rapidly shift into location and accumulate at the tips of the severed axon, mediating fusion for segment reconnection. The combined effects of EFF-1 and AFF-1 promote dendritic repair due to the disrupted connection from the severed axon afterward. With more research, Wallerian degeneration, the active degeneration of the neuron distal from the injury site caused by damage to nerve fibers, can be more easily prevented [4]. The graphic below further explains how the mentioned glycoproteins facilitate axonal fusion after transection.

![Diagram](image)

**Figure 1.** This diagram shows the fusogens and other molecules involved during axonal fusion and where they accumulate on both ends of the severed axon [4].

**Polyethylene Glycol for Spinal Cord Injuries**

Moving from minor neuronal injuries, spinal cord injuries (SCI) on the other hand disrupt motor, sensory, and autonomic functions within the body. There are no clinical treatments successful at repairing the damage to restore motor function. However, a relatively inexpensive and water-soluble polymer has been researched for its potential benefits in medicine. Polyethylene glycol (PEG), a fusogenic chemical, has been noted for immediately repairing physical damage, promoting
Axonal regeneration, restoring synaptic connections with target tissues, and overall, stimulating injury repair. It can repair compromised neuronal membranes by fusing the cell membranes together. Although this fusion process is unclear, there are two hypotheses as to how it occurs: PEG dehydrates the involved cell membranes which allow lipid elements to cross over into each other, or PEG reduces the surface tensions and improves both membranes’ fluidity so they seal to each other [5]. Either hypothesis requires the general prerequisite that the two involved membranes are in close proximity [6]. This allows for their phospholipid membranes to rearrange together by cell-aggregating agents or to diminish repellent charges between the two membranes by using membrane-modifying agents which change the individual surface charges [7].

After SCI or any damage to the central nervous system, a glial scar forms around the injured area in order to protect it, inhibiting the growth of new axons and synapses. Certain biomaterials have been able to fill these lesions, delivering new cells to replace the dead ones, or to release drugs which improved damage from inflammation and increased cell invasion [5]. Current techniques of nerve injury repair do not address the physical disruption in the axonal membrane [8]. However, PEG was discovered to immediately repair physical damage in the spinal cord, reducing local glial scar formation in a five-step process: trimming of severed ends, prevention of plasmalemma sealing, rejoining the segments with microstructures. This results in the inducement of membrane fusion between segments with PEG, repairing residual membrane disruptions mediated by vesicles [4].

Although the use of polyethylene glycol in medical settings is premature, multiple laboratory and clinical trials have proven successful. Ren et al. performed laminectomies at the T-10 vertebra in rats. Immediately, PEG was directly applied to the transection point while the control group received saline applications. The goal was to refuse the thoracic spinal cord. Over a period of 28 days, the PEG-treated group showed better blood-brain barrier scores than the control group. The PEG-treated group showed signs of recovery in increased somatosensory evoked potential (SSEP) waveforms while the saline-treated group showed no improvement. Direct tensor imagery showed that the significance in differences of recovery between the PEG and saline-treated groups were possibly affected by the tissue continuity that the PEG was able to achieve in refusing the spinal cord. Ren et al. noted that PEG did not actually prevent the formation of the glial scar, but by promoting axonal regeneration, the severed spinal cord ends were able to bridge together, improving function restoration. Liu et al. applied PEG at the transection site of the spinal cord of a dog at T-10. On a scale of 0-15, 0 being no hindlimb movement, the PEG-treated group had a median
blood-brain barrier score of 8, whilst the control group had a median score of 3. Tensor imaging showed fiber reconstitution of the spinal cord and increased SSEP waveforms in the PEG-treated group. Kim et al. conducted cervical laminectomies at C5 in rats to model SCIs and then applied PEG or saline. Motor-evoked potential (MEP) measurements showed increased amplitudes at only 1 hour after the injury. The results for the PEG trials for SCIs in animals suggested additional benefits of early and direct application of PEG to the transection in the spinal cord which would lessen neural damage and further the regenerative process [5].

In 2016, Bamba et al. were the first to clinically-use PEG-fusion in humans. They were able to repair four fingers of two teenagers after complete nerve transection injuries, and within twelve hours, the nerves were fused with the five-step process. The success of the PEG-treatment sparked discussion over its potential usefulness for all human nerve injuries. Not only could it be applied to the spinal cord, but its different applications could expand into the peripheral nervous system to aid in functional recovery for all nerves [4].

**Amyloid-β Cells for Alzheimer’s Disease**
In other cases, fusogens have been determined to actually be more harmful to our nervous system. Alzheimer’s is a neurodegenerative disease leading to progressive loss of memory and overall cognitive decline, resulting in death. Even though it is one of the most studied pathologies, it is not fully understood on a molecular level and there is no available cure. However, it has been discovered that patients with Alzheimer’s have extracellular deposits of amyloid β-peptide (Aβ) within the brain that are generated from the proteolytic cleavage of the glycoprotein, β-amyloid precursor protein (APP) [9]. These cells are neurotoxic and are thought to play a major role in neural cell death brought on by Alzheimer’s through the disruption of cellular activity; Aβ-peptides mediate membrane fusion and induce high membrane responses such as structural reorganization. They directly change the biophysical properties of cell membrane fluidity by modifying membrane fluctuation, fusion, and transformation and disrupting vital organelle activities, like mitochondrial fission and fusion [10]. Overall, virtually all pathobiology researchers for Alzheimer’s disease, over the last 15 years, support the hypothesis that almost all forms of Alzheimer’s disease are initiated by the progressive cerebral accumulation of Aβ-protein which sets-off a multicellular cascade that results in microgliosis, astrocytosis, neuritic dystrophy, neuronal dysfunction, neuronal death, and synaptic alterations that lead to impaired neurotransmitter activity and cognitive function. One benefit of this hypothesis is that it lays out specific molecular targets that can be screened against to develop treatments to prevent Alzheimer’s disease by preventing cerebral β-amyloidosis [13].

Conclusion

The clinical use of fusogens for medical treatment is still in its beginning and experimental stages. However, in-depth research has proven that these membrane-fusion inducing glycoproteins have the capacity to make axonal fusion more efficient and to reverse spinal cord injuries, as well as to better treat Alzheimer’s disease. With more experimentation, fusogens may well become standard and successful treatment options for these fatal diseases. This article only analyzed the treatment potentials of four fusogens: Epithelial Fusion Failure-1 and Anchor cell Fusion Failure-1 for axonal fusion, polyethylene glycol for spinal cord injuries, and amyloid-β for Alzheimer’s disease. More research and study expansion into the effects of other glycoproteins has the potential to reveal even more potential benefits of fusogens and possibly bring about groundbreaking treatments for widespread disorders.

References


Music as a Viable Therapeutic Treatment Option for Alzheimer’s Disease

Pranav Ramesh

Abstract
As the sixth leading cause of death in America, Alzheimer’s has taken the livelihood of millions of people, and this number keeps going up [1]. Currently, the scientific community has turned to medication-based treatments in order to decrease the presence of the negative symptoms that Alzheimer’s entails. However, one might say these efforts are at no avail, as the number of cases is on a track of exponential growth. People with the disease face a plethora of mental health disorders, and the caregivers and loved ones of these people are living in suffering. Instead of trying to tackle the disease head-on, health care professionals and caregivers are exploring the efficacy of non-pharmacologic treatments, such as music-based intervention programs. This article seeks to explore findings in the field, analyze them, and propose methods of implementation.

Pathology of Alzheimer’s Disease

Alzheimer’s disease is an extremely debilitating neurodegenerative disease that results in gradual but severe memory loss, cognitive function decline, loss of personality, and the inability to perform basic tasks necessary for everyday life. Currently, the precise cause of the disease is unknown, but researchers have found a strong correlation between the presence of amyloid plaques as well as hyperphosphorylated tau protein clusters (known as neurofibrillary tangles) with Alzheimer’s disease. These amalgamations of proteins interact with the physiological structures of the brain in an unknown manner and ultimately contribute to the development of Alzheimer’s [2].

Considering that the specific cause of the disease is unknown, drug development companies and researchers have been focused on utilizing symptomatic therapies. These drugs and treatments objectively resolve some of the symptoms of a disease, rather than the direct causes. Most doctors and healthcare providers are prescribing drugs that act as

Figure 1. A comparison between brains in different stages of cognitive ability [3]
cholinesterase inhibitors, such as donepezil and galantamine, for people with varying degrees of severity of Alzheimer’s and other forms of dementia [4]. There are a plethora of other drugs being constantly tested, but the effectiveness and safety of them are still in question. Moreover, many antipsychotics prescribed to Alzheimer’s patients have been linked to causing higher mortality [5]. Surprisingly, many people with Alzheimer’s become more prone to mental health issues as a side-effect of taking these medications, because of the constant physical side effects that occur such as diarrhea, nausea, and vomiting [6].

As a result of the many abnormalities present in the brain from the pathology of Alzheimer’s, researchers are still in debate about how to approach future treatments, specifically pertaining to the timeline of cognitive decline. Medications with the goal of targeting different physiological abnormalities are currently underway in the development process. In the meantime, however, it is of utmost importance to preserve the emotional wellbeing of patients, as many people with Alzheimer’s are greatly suffering from a mental health standpoint. It is in this effort to ward off mental health issues that researchers are touting the potential efficacy of integrating music as an alternative therapy to help treat Alzheimer’s [7].

Current Research on Music and Alzheimer’s

Many researchers who have opted to treat Alzheimer’s with a more holistic approach in mind draw inspiration for potential therapies by focusing on the emotional, rather than the physiological state of Alzheimer’s patients. This has led them to conduct a variety of quasi-experimental trials, randomized control trials, and other intervention studies on therapies like group reminiscence therapy, pet therapy, and music therapy [8,9]. However, there has been some evidence that music might act as a significant non-pharmacologic intervention.

One of the most popular reasons why music has been selected as an effective therapy is due to its unique relationship with a person’s memories. Researchers specifically believe that music engages memory centers that are separate from the traditional memory centers of the brain. This relationship between music and memories has been well documented and became an integral component of Oliver Sacks’s work. Sacks, a highly-acclaimed neurologist, was one of the key figures in the application of music to treat Alzheimer’s. In the media, he has starred and created many documentaries and shows which showcase how credible the anecdotal evidence for music therapy is. Notably, he has been featured in prominent documentaries such as Alive Inside. These forms of media have been critical in shedding light on the potential that music brings to the table in terms of treating Alzheimer’s. In many cases, people with Alzheimer’s who were otherwise sedentary or non-reactive to stimuli, were able to carry out full conversations with caregivers about their past, especially childhood experiences and memories with strong musical associations. Comprehensive reviews of research literature support this. Researchers suggest that the “emotional resonance” of music essentially transports people to specific memories by utilizing the pre-existing structures in our brain that make us feel good [10].
To explain the presence of these memory associations, researchers have been extensively digging to find out what is occurring on a physiological level. By utilizing imaging tools, such as functional MRIs and PET scans, scientists have been able to get a grasp of the degree to which music affects the neurophysiology of Alzheimer’s patients [11]. According to research done regarding the neurophysiological effects of music, music activates a variety of different systems in the brain corresponding to different functions at the same time. Parts of the brain controlling fine motor movements, haptic feedback, and emotional arousal all activate at once when listening to music [12]. Part of the reason why scientists believe that music allows for increased communication in patients with Alzheimer’s is because it enhances speech, verbal interpretation, and attention span. Due to so many cognitive functions being utilized and activated at the same time, when listening to music, patients experience a wide range of benefits for a considerable amount of time even after listening to music.

**Implementation of Music Into Alzheimer’s Treatment**

A variety of methods have been proposed pertaining to precisely how music should be implemented into Alzheimer’s care. One method in particular covers the specific genres of music that yielded the best results among patients. In a study published in 2020, this specific subject matter was extensively researched. Researchers determined how multicultural music impacts six key aspects in a socioeconomically, culturally, and cognitively diverse community of older adults. After combing through hundreds of recorded interactions that people with Alzheimer’s had with music as well as interviews with study participants, researchers were able to come to a key conclusion. Religious music, especially that of which was exposed to the person with dementia at a young age greatly improved cognitive function, communication skills, and triggered better relationship building between them, loved ones, and caregivers. In order to reap these benefits however, the environment of the patients should be carefully curated [14].

Whether the patient is living in an assisted living facility or memory care center, it is imperative that the music they are exposed to is personalized to yield the best results. Through either family or friends, caregivers need to discern the patient’s favorite types of music from different periods of their life. The reason musical memory seems to be extraordinarily unique is because of the strong emotional connections that are formed between events, the song, and
emotions experienced during that time. This consequently results in relatively vivid recollections and periods of reminiscence that these patients would regularly not be able to experience. Within these personalized playlists, music connecting the person to their faith or religion should also be included. The study mentioned in the previous paragraph above supports this assertion, as it has been found that listening to this type of music reinforces self-identity and values, therefore allowing for better emotional stability and elevated mental wellbeing. Interesting studies have also been done to determine the effects that music and meditation have on certain biomarkers in people’s blood that may be indicative of cognitive decline or dementia. Researchers found that the participants who exhibited high practice adherence to interventions (Kirtan Kriya Meditation and Classical music listening) saw significant increases in telomerase activity, telomere lengths, and higher levels of Aβ peptides, all of which result in higher cognitive function, less stress, and an overall higher quality of life [15].

To create similar results that participants in the program have experienced, it could be highly beneficial for memory care homes to implement these interventions as actual therapies, rather than for research purposes. Even if they follow the exact same intervention methodology that was performed in the aforementioned research, people suffering from Alzheimer’s are highly guaranteed to experience positive benefits. These benefits can be expounded by using personalized music instead of standardized classical music. As shown by the research I have conducted, this will not only physiologically improve the patient but will greatly increase their emotional well being .

Conclusion

With Alzheimer’s becoming one of the greatest pathological threats that humanity faces, it is all the more important to take a chance with other symptomatic therapies that are not all pharmacologic interventions. This has the potential to drastically increase the quality of life of people suffering from Alzheimer’s and is backed by substantial empirical research and findings. Although some dismiss the benefits as pseudoscience, it is time to get serious about utilizing non-pharmacologic interventions like music that have been proven to be successful and to help in the treatment of Alzheimer’s. It might not be the perfect cure, but at least we can allow people with the disease to lead more peaceful and happier lives.

References


Using Boron Neutron Capture Therapy to Combat High-Grade Gliomas

Vasu Shandar

Abstract
This paper takes a broad lens concerning the development and progress of Boron Neutron Capture Therapy (BNCT) in the past 50 years. BNCT has proven to be a viable approach to treating high-grade gliomas and other brain and neck tumors in situations where other treatment options have failed. Visibility of BNCT as a treatment has been limited because of the complex facilities required to carry out the process; however, this paper analyzes the future for commercializing BNCT for treatment and improving access and safety for its use.

Introduction
Boron Neutron Capture Therapy is a method to target and destroy tumors in the head and neck region, most commonly glioblastomas in the brain. BNCT mainly functions by delivering boron particles to tumor cells and irradiating the region with neutrons to kill the tumor cells. When Boron-10 isotopes are irradiated by neutrons, the reaction results in a high energy alpha particle and...
a recoiling Lithium-7 molecule being released. Alpha particles have a short pathlength, which means their destructive properties are limited to tumor cells. Thus, in theory, if boron particles are selectively delivered to tumor cells, irradiation can allow alpha particles to destroy only tumor cells while sparing healthy cells. This treatment option is contingent on two processes. First, the boron must be selectively delivered to tumor cells and second, the neutrons used for irradiation must be administered in the optimal dosage to kill tumor cells and spare healthy cells. The future of BNCT is one where patients with head and neck tumors have the potential to be cancer-free in a single BNCT session. This paper will review the history of BNCT and evaluate the success of different approaches to optimize the two key processes for commercialization.

History and Methodology

BNCT was identified for its potential almost immediately after the discovery of the neutron by G.L. Locher in 1936. However, only by 1951 were clinical trials in place at MIT and Massachusetts General Hospital (MGH) [2]. These studies utilized fission reaction beams of thermal neutrons. However, this method proved to be inadequate for penetration. This limitation led to clinical trials being paused for decades until the early 1990s. When the trials restarted, higher energy neutrons were utilized and penetration into the brain was optimized to reach tumors. Extensive clinical trials have proven two drugs to be the most effective delivery methods to date. However, limitations within each still exist. The first drug is boronophenylalanine (BPA), synthesized by Snyder, while the second drug is sodium borocaptate (BSH), first used by Hatanaka in Japan [2]. Both drugs have been criticized because of their variability in tumor uptake. Variability in tumor uptake can cause treatment to be ineffective for some while successful for others, with no metric to control this success rate. The most favorable results of BNCT using BPA and BSH have been achieved at the Kyoto University Research Reactor Institute (KURRI) [2]. Out of the 49 patients with unresectable tumors at the institute, 80% had failed chemotherapy. After BNCT, the one-year survival rate rose to 58% for those with unresectable tumors and 41% for those with recurrent tumors [2]. The clinical trials at KURRI utilized a mixed dosage of BPA and BSH, allowing the treatment to be maximally effective. Even in cases where chemotherapy is a viable treatment option, other studies at KURRI have proven BNCT to be competitive with chemotherapy while only requiring a single BNCT session. Thus, the future of BNCT likely falls in filling the niche of patients where surgery and chemotherapy have already failed. However, since one of the underlying conditions for the success of BNCT is selective delivery of a lethal dosage to tumor cells, the next section will focus on recent developments in the delivery options for boron-10 to tumor cells.

Development in Delivery Methods

The conditions for a delivery agent for BNCT are that they must have a low inherent toxicity, high tumor uptake, and easy clearance from the normal blood tissue [3]. The delivery of the agent must also easily pass the blood-brain barrier which is the selective layer of endothelial cells that regulates solutes in the blood from passing into the fluid of the central nervous system. Finding a delivery agent that can cross this barrier is a major impediment to BNCT research [4]. BPA's mechanism for targeting tumor cells is upregulated amino acid transporters in cancer cells. The
rapid proliferation rate of cancer and tumor cells causes them to require more amino acids to keep pace with cell growth. To provide the necessary levels of amino acids, the tumor cells upregulate amino acid transporters, creating a prime target for BPA. New studies use the same mechanism of upregulated receptors to target tumor cells. For instance, one study by Backer focuses on using peptide ligands to target one of two specific receptors: either the vascular endothelial growth factor (VEGFR) or the epidermal growth factor receptor (EGFR) [5]. However, the issue with the targeting of VEGFR and EGFR is the requirement of multiple rounds of BNCT to effectively reach all tumor cells. There are still multiple other different strategies for delivery being investigated right now. One interesting study in effect is the use of boron nitride nanotubes (BNNT) as delivery mechanisms with folate-receptor functionalized coating for the BNNTs. Folate receptors have been proven to be over-expressed in tumor cells in multiple studies because of folate’s key role in DNA replication and cell division. The BNNT molecules can travel easily through the blood while the functionalized folate coating allows the BNNT to only reach tumor cells [6]. Other current studies for optimizing boron delivery use nucleotides, amino acids, and liposomes. Despite these studies, BPA and BSH are the only drugs that have been approved for clinical use in the past 50 years [3].

Developments in Neutron Supply

Another impediment for using BNCT to combat brain tumors is the complex neutron supply it requires, which is unsuitable for implementation in hospitals due to safety concerns. Fission reactors are the current neutron source of choice because of their capability to produce high energy neutrons for the boron reactions. 8 reactor facilities have been built in the Americas, Europe, and Asia for clinical use in BNCT [2]. These reactors have safety issues with radiation, barring them from being viable in urban settings or hospitals. However, in China, scientists have constructed a reactor designed for neutron capture therapy use, and it is suited for urban settings because of its use of low power core neutrons. Accelerator-based neutron sources are a new development that produce low-intensity neutron fluxes [2]. While the low intensity of accelerator sources makes it less competitive than fission sources, due to a decreased ability of the neutrons to reach the tumor targets, accelerator-based neutron sources are more compact, less expensive, and safer.

Future of BNCT

Overall, Boron Neutron Capture Therapy is a treatment with high potential for helping individuals in cases where chemotherapy or re-irradiation has failed. However, a few key issues must be addressed before BNCT can be successful on a large scale. Progress has been inhibited because of a lack of communication between different institutions doing BNCT research. BNCT is still considered experimental because of a lack of standardization for radiation calibration or treatment plans [2]. Currently, there is no consensus on dosage recommendations. To conduct large scale clinical trials, there needs to be dosage uniformity across institutions conducting BNCT research [2]. Furthermore, BNCT cannot reach deep-seated tumors in the brain currently, limiting its usage to shallow glioblastomas. There is also no mechanism to predict which patients are most likely to respond favorably to BNCT treatment. However, despite current setbacks, the optimization of delivery techniques and commercialization of neutron sources can provide major progress for
widespread clinical trials. With these developments, BNCT can fulfill its full potential of helping patients with brain tumors where other methods have failed.

References


Parkinson’s Disease: Exploring Levodopa’s Effectiveness as a Treatment

Bibek Samal

Abstract

Treating Parkinson’s Disease has always been a struggle for clinicians and researchers, as there still is no known cure for the disease. A Parkinson’s diagnosis often implies a lifetime of medications and physical therapy. For many years, chiefly one treatment has been proven as immensely successful in inhibiting some of the symptoms associated with Parkinson’s for certain periods of time. This therapy, termed levodopa (L-Dopa) therapy, the brainchild of pharmacologist Arvid Carlsson, has been held to a high standard of symptomatic inhibition by increasing dopamine concentration, the primary neurotransmitter associated with movement. In addition to levodopa, there are other treatments, such as deep brain stimulation, and medications, such as benztropine and selegiline (an anti-tremor medication and antidepressant respectively) [6]. This article aims to highlight the effectiveness of L-Dopa as a treatment for Parkinson’s and also study some of the other medications and therapies that are being used to combat the disease and their viability.

Background & Physiology

Parkinson’s Disease is a neurodegenerative motor disease associated with the central nervous system, inhibiting movement. A review of the pathophysiology of Parkinson’s shows the buildup of misfolded proteins called Lewy bodies, which consist of alpha-synuclein [1]. This near-fatal disease works by degenerating the region of the brain called the substantia nigra, which is connected with the basal ganglia, the brain’s region associated with behavior and movement. This degeneration leads to the death of motor neurons, nerve cells necessary for movement, and eventually results in some of the common motor-impaired symptoms such as tremors, balance problems, and bradykinesia (a slowness of movement) [1].

Although no cure is available, treatments have been introduced for Parkinson’s, the most prevalent approach being the use of levodopa. Currently, the use of levodopa is regarded as the foremost approach to treating Parkinson’s disease. Levodopa functions by crossing the blood-brain barrier and increasing dopamine concentrations in order to promote movement [2]. In Parkinson’s
patients, dopaminergic neurons eventually die, thus not generating movement within the body \[2\]. This inability to generate movement is what leads to the degeneration of motor neurons and introduction of motor symptoms within the substantia nigra. By stimulating dopamine generation, this medical therapy is a key contributor to restoring movement in patients. Similarly, other options are becoming more widely known and tested such as deep brain stimulation and dopamine agonists \[2\].

These recent and experimental treatments target areas of the brain such as the subthalamic nucleus and adjacent regions in order to test the effectiveness in areas different from the substantia nigra. The next sections examine the benefits of the mentioned treatments and how each approach is applied to the different range of symptoms that the patient experiences.

**Choice of Treatment Based on Stage**

Not every treatment will have the same effect on patients based on their symptoms. Treatments and approaches are best modeled for the patient based on the progression and stage of the disorder. Parkinson’s Disease usually occurs in 5 stages with increasing severity of symptoms in each stage.

![The mechanism of Parkinson's disease medications](image)

*Figure 1. Cell signaling pathways for different Parkinson’s Disease treatments [6]*
The first stage is characterized as very mild and includes symptoms such as a light tremor, rigidity, and stiffness on one side of the body. In this stage, symptoms occur very mildly, thus the doctor may wait for symptoms to progress in order to make a clear diagnosis. Because of this, seldom any medications are prescribed in this stage. Moving into stage 2, symptoms start to appear bilaterally (on both sides of the body), introducing the difficulty of moving and more apparent tremors. Stages 3 through 5 continue the progression of the appearance of tremors and increased loss of balance. These stages mark the increasing difficulty of movement and inhibition of basic motor tasks such as voluntarily grasping and walking [7].

Starting with the first two stages, theoretically, the most used approaches are levodopa therapy and carbidopa. Levodopa acts as the primary line of medications after diagnosis and treats the wide range of symptoms throughout the stages. Since levodopa increases dopamine levels in the brain, this lowers the occurrence of akinesia, the symptom of jerking involuntary movements. Similarly, levodopa also helps to treat the primary symptom of tremors that is more widely observed. However, levodopa also causes side effects such as vomiting and nausea, which occur due to the added depletions of “serotonin, thiols, l-tyrosine, and l-tryptophan”, resulting in a nutritional deficiency [1]. Because of this, levodopa is usually paired with carbidopa, a decarboxylase inhibitor, which inhibits pyridoxal 5’- phosphate-dependent enzymes, decreasing the risk of nausea [3]. However, just as levodopa has downsides by acting without carbidopa, carbidopa has significant downsides as well, causing the fatal symptom of irreversible dyskinesia. Dyskinesia refers to the uncontrolled, involuntary movements that patients feel during the onset of Parkinson’s. According to Hinz, Stein, and Cole, “Research into the phenomenon led to the formulation of the hypothesis that if significant depletion of histamine induces dyskinesias, then carbidopa is capable of inducing dyskinesias, which if not managed properly may be perceived as irreversible” [3]. Thus, this establishes carbidopa is a histamine depleting agent, which is the cause behind the increase of dyskinesias.

**Levodopa’s Toxicity and Other Advanced Symptoms**
Moving forward, levodopa has significant downsides even though it is regarded as the key player in the fight against Parkinson’s. For example, levodopa is a nausea-inducing agent, needing to be paired up with carbidopa in order to prevent its breakdown before crossing the blood-brain barrier and losing effectiveness. Following this, levodopa has also had a history of accelerating or increasing the occurrence of certain symptoms of Parkinson’s Disease, such as dyskinesia. Looking at one instance, “In the early 1990s, a number of in vitro studies demonstrated that high doses of LD can be toxic to dopaminergic neurons in cell culture, causing some PD specialists to recommend withholding LD for as long as possible” [2]. This signifies that levodopa has an optimal dosage at which it performs the most effectively, decreasing its therapeutic benefits if exceeded that amount. In clinical settings, this serves as an observance that pharmacological therapies have their limitations in patient deliverance.

Similarly, the drug deliverance also depends on detailed patient situations. The regulation of levodopa is different per each patient that takes it since their bodies respond differently, due to factors related to age and other health ailments. This is evident in clinical scenarios as, “Clinicians should discontinue the medication in patients that experience excessive daytime sleepiness. Long-term use of levodopa presents with other complications. The quality of life of patients can be negatively affected because of irreversible motor function changes from drug use” [4]. Looking at this particular information, levodopa has severe limitations on different individuals based on past medical histories, making it difficult to gauge a universal optimal amount of medical usage.

Looking at this problem pathologically, cells begin to undergo apoptosis (cell death) with the formation of “free radicals” [3]. With this process, regular healthy cells are marked for degeneration when levodopa enters the body. Because of this debilitating issue, clinicians should double-check all patient histories and ensure that levodopa will be used correctly within the body.

**Conclusion**

With the advent of levodopa and complementary medications such as carbidopa, treatments for Parkinson’s Disease are plentiful and portray a great deal of research. Levodopa is one of the most advanced treatments for aiding patients in all stages of Parkinson’s disease. Its pharmacological properties such as the central conversion to dopamine after crossing the blood-brain barrier are key in reversing symptoms of the disease. However, as levodopa has its downsides, other approaches such as carbidopa and dopamine agonists (promoters) can be used either to complement levodopa or to act as a substitute. Symptoms such as nausea, vomiting and dyskinesia were mentioned with the use of raw levodopa, thus clinicians can pair this up especially with carbidopa [3]. In conclusion, levodopa is one of the key therapies advancing the fight against Parkinson’s disease and is instrumental in slowing its progression. To potentially counter its downsides and ensure maximum potential, the medication should be deliberated by clinicians based on the disease stage that the patient presents with as well as the patient’s medical history.
References


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