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FEATURED ARTICLES

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INTERNATIONAL YOUTH NEUROSCIENCE ASSOCIATION
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GENERAL NEUROSCIENCE

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Marijuana, a popular substance, can cause underdevelopment in the brain. The last 10% brain remodeling necessary to acquire the adult brain size happens during adolescence, in which changes occur in the prefrontal cortex of the brain. The prefrontal cortex is responsible for decision making, controlling impulses, and solving problems. The use of marijuana during adolescence can cause the death of overproduced cells and synaptic pruning (when extra neurons and synaptic connections are eliminated to improve neuronal transmissions), and higher blood flow in the brain in males. A higher blood flow in the brain indicates acute hypoxia: low oxygen in the tissues. The substance that causes the psychological effects of marijuana is called Delta-9-Tetrahydrocannabinol (THC); when consumed, it moves from the lungs to the bloodstream, in which blood carries it to the brain. The long-term side effects of marijuana on adolescents include an abnormal brain shape, loss of IQ points, a decreased ability to function, an increased chance of lung cancer, and respiratory issues. Although marijuana use is common, treatments for substance use disorders are limited; there is a room for improvement in treatment for substance use disorders.

LSD vs. Heroin: Different Drugs with a Notorious Past Donya Atashie pages 9-14

This article focuses on two Schedule I drugs - LSD and Heroin that have different impacts on the brain but are connected by the similar ability to have caused chaos in the nation by their excessive usage. LSD being a hallucinogen binds to the (5-HT2A) serotonin receptor which indirectly affects the dopamine levels in the body. The LSD crisis took place in the 1960s during “The Summer of Love” or the hippie movement. In recent years there has been an opioid epidemic including that of heroin. Heroin directly binds to the opioid receptors present in the brain and alters the reward system.. In case of LSD, the serotonin receptors are responsible for the hallucinogenic effects caused during an acid trip. A mere 100 micrograms of the drug can lead to effects lasting longer than 12 hours. Physical effects of using LSD include sweating, synesthesia etc whereas the long term effects include HPPD, schizophrenia and long term hallucinations. In case of Heroin the stark physical effects include withdrawal symptoms, vomiting while the long term ones include inflamed brain, organ failure and possible development of Alzheimer's Disease.

Theory of Mind: The Human Brain & Artificial Intelligence Shrivibha Lanka pages 15-17

The theory of mind (ToM) is a cognitive theory that helps us understand others and solve problems, namely,
our ability to seemingly predict our peers’ actions and emotions. ToM is similar to artificial intelligence in that it aims to infer and predict outcomes. However, ToM in the human brain predicts human responses and actions, whereas artificial intelligence employs methods such as machine- and deep learning to interpret data in computers so as to mimic the human brain. Artificial intelligence should be limited such that it does not replace the human theory of mind, as it might lead to uncontrolled development of computing devices.

**DISEASES AND DISORDERS**

**Current and Emerging Treatment Options for Hepatic Encephalopathy: A Systematic Review and Meta-Analysis Summary**

Shiv Krish Jaidev Mehta, Mandeep Chahil, MD

Hepatic Encephalopathy is the result of a damaged liver, leading to the destruction of certain brain functions. With thousands of individuals every year inflicted with Hepatic Encephalopathy, new treatments are constantly being developed and used to ease and reverse the damage caused by this disease. Through Shiv Krish Jaidev Mehta and Dr. Mandeep Chahil’s article, readers will learn more about the current and developing treatments for Hepatic Encephalopathy, examining both the practical and clinical considerations when treating a patient with Hepatic Encephalopathy.

**Naegleria fowleri: The Brain-Eating Amoeba**

Ginger Z. Watzinger

N. fowleri is a thermophilic amoeba causing primary amoebic meningoencephalitis, an infectious disease with a high mortality rate. The microorganism initially damages neuronal, glial and immune cells found in the olfactory epithelium, then it attacks the central nervous system. The damage triggers a range of symptoms, including headache, fever and loss of consciousness; however, these only appear days after the initial infection when the destruction is irreversible. The combination of delayed symptom onset and complicated diagnosis process severely decreases the likelihood of successful treatment; yet, a case study demonstrates that recovery is possible with early intervention.

**Sigma-1 Receptors: Promising Therapeutic Target for Alzheimer’s Disease**

Aleena Kuriakose

Alzheimer’s Disease is a progressive neurodegenerative disorder that causes severe cognitive impairment leading to a decline in memory, comprehension and reasoning. Sigma-1 receptors, one of the two sigma receptor subtypes, are multifunctional ligands present in the endoplasmic reticulum which can act as promising targets for the treatment of AD. Dysregulation of IP3Rs may be credited to the pathology of many diseases such as heart disease, exocrine secretion deficit, taste perception deficit, and neuronal degeneration. The sigma-1 receptors act as intracellular receptors, serving as chaperone proteins that regulate Ca2+ signaling through the IP3 receptor; activation of the sigma-1 receptors results in many neuroprotective properties, including the alleviation of ER stress and modulation of calcium influx. They also promote neurogenesis in the hippocampus. Sigma-1 receptors have become promising therapeutic targets for the treatment of AD as the activation of these receptors regulate calcium homeostasis conferring neuroprotection. The article concludes by saying that the sigma-1 receptor has been shown to potentially
inhibit or even reverse amyloid-β oligomer-induced toxicity and block their signal transduction.

Neurological Impairment in Duchenne’s Muscular Dystrophy and Its Treatment

Anirudh Kannan

Duchenne’s Muscular Dystrophy (DMD), one of the most common genetic disorders, is a mutation that causes the absence of the protein dystrophin, responsible for strengthening smooth and cardiac muscle fibers. Individuals with this disorder suffer from muscle weakness and heart problems (cardiomyopathy). The neurological symptoms include speech and learning disabilities. The life expectancy of patients with DMD is 27 - the cardiovascular problems become more difficult to handle after hitting their late 20s. An animal model for the disorder, the exon-52 deleted mouse, demonstrated that impairment in DMD is progressive with increasing brain volume. Dp71, an isoform of DMD, plays a major role in cell division, demonstrating significant decrease in cell growth as the Dp71 expression decreased. Interestingly, a study found that the Full-Scale Intelligence Quotient (FSIQ) of DMD patients is lower than that of a control sample; differences in the FSIQ depending on the location of DMD were also found. Currently, there are three treatments for DMD, in which all three involve some form of exon skipping (gene therapy that involves RNA splicing); studies to bring the Adeno-Associated Virus (AAV) into a treatment for the DMD are being made: if done correctly, this modification can produce dystrophin to treat DMD.

Scrupulosity: An Overview of “Religious OCD”

Katherine Kaufman

Scrupulosity affects as many as one third of people with obsessive-compulsive disorder in the US. Multiple structures of the brain are involved in the condition, including the orbitofrontal cortex, cingulate cortex and basal ganglia, as well as hyperactive neuronal circuitry. However, it is difficult to establish the relationship between the structural abnormalities and the disorder, as well as the role of underlying risk factors. While the symptoms of scrupulosity are generally well studied and understood, a culture of stigma surrounding its nature often leads to misdiagnosis in many patients and may even interfere the treatment process. When recognised, it is treated psychotherapeutically or pharmacologically, whereas more modern technological approaches may help those who do not respond to the traditional methods.

Investigating ASD Through a PCT Lens

Arushi Dinker

Autism spectrum disorder (ASD) is a developmental disability that drives challenges in socializing, behaviour, and communication. Predictive coding theory (PCT) suggests that our brain generates predictions about the world to evaluate incoming sensory information from the environment. To elaborate, PCT suggests the brain anticipates sensory information by generating a template against it and comparing the incoming information to that template. From a PCT perspective, if individuals are unable to detect and learn predictive associations, their predictions will inhibit them from performing well in interpretive situations. Moreover, if one can form predictions but not employ them, erroneous information may be used to update predictions, which has possible applicability and implications for individuals with autism. Better understanding the role of PCT in autism would greatly benefit ongoing research evaluating possible courses of care.
Human brain organoids (HBOs) are three-dimensional in vitro structures that imitate the development of the human brain; they are developed from human induced pluripotent stem cells. Efforts have been made to evaluate consciousness in HBOs, investigating their moral relevance and proposing frameworks for their ethical usage. Methods of consciousness detection may include observing an HBO’s structure, as well as its Perturbational Complexity Index. Moreover, HBO transplants engender unique issues, such as possibly making host animals more vulnerable to suffering subsequent to in vivo transplantation. Proposed ethical frameworks suggest allowing HBOs when benefits seemingly justify the suffering inflicted in an experiment, which itself must be minimized. However, such frameworks need complete regulations and established knowledge before implementation.
Dear Readers,

Welcome to the first installment in the sixth season of the IYNA Journal! Summer break is almost over and class will soon resume. For many of our readers, the quest for more knowledge about the brain never stops. We’re glad that you all have taken the time to learn about fascinating neuroscience topics in this month’s release.

In this issue, we are proud to publish the work of students from around the world. As we progress into a new school year, the quality of articles submitted to the IYNA journal has only risen. We would just like to thank everyone for their dedication and commitment to informing readers about the vast realm of neuroscience. With that being said, here are some previews of the essays published this month:

Reeve Kotha provides an overview of the neurological effects caused by marijuana on the brains of adolescents, Shiv Krish Jaidev Mehta discusses the treatment options for hepatic encephalopathy, and Yue Yu sheds light on the ethical quandaries behind human brain organoids.

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

Best Regards,
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Cannabis: Its Effects on Adolescents’ Brains

Reeva Kotha

Abstract
Marijuana is the second most used substance by adolescents, leading to many cognitive impairments and neurological deficits. However, it is not well understood how marijuana underlies these defects. In a 2017 Youth Risk Behavior Surveillance Study, it was found that 36% of 9th-12th graders in the United States use cannabis. The overall growth of an adolescent is crucial during these years, signifying that the use of marijuana will significantly impair some important bodily functions. This article discusses side effects and treatments for marijuana alongside the neurological effects of the substance on the adolescent brain.

Brain Anatomy of an Adolescent Without The Use of Marijuana

When kids are around six years old, they have reached 90-95% of their adult brain size, meaning that the last 10% of their brain remodeling is critical. The brain remodeling happens intensively during the adolescent stage and continues until they are in their early 20s. During this time, brain development is crucial to the growth of teenagers. One of the most significant changes during adolescence is in the front of the brain, the prefrontal cortex, which is responsible for decision making, controlling impulses, and solving problems. Until the prefrontal cortex is developed, teenagers often rely on their amygdala, which is associated with emotions, impulses, aggression, and instinctive behavior.

Brain Anatomy of an Adolescent After Using Marijuana

According to Wilson and colleagues (2000), “individuals reporting marijuana use before age 17 demonstrated decreased whole brain and cortical gray matter in addition to increased percent white matter volume. Findings also included higher cerebral blood flow in males reporting early initiation of marijuana use [5].” Higher cerebral blood flow suggests acute hypoxia, low oxygen in the
tissues. The use of marijuana can also lead to the death of overproduced cells and synaptic pruning, the process by which extra neurons and synaptic connections are eliminated to increase the efficiency of neuronal transmissions. [6]

THC

Delta-9-Tetrahydrocannabinol, also known as THC, is a psychoactive substance that is found in cannabis plants. This chemical is responsible for marijuana’s psychological effects. When someone uses marijuana, delta-9-tetrahydrocannabinol (THC) passes into the lungs and goes into the bloodstream. From there the blood will carry THC to the brain. The body absorbs THC at a faster rate if that individual does not consume any food or liquid. THC can be smoked by hand-rolling cigarettes, pipes (bongs), and blunts, which are emptied cigars that have been partly or completely refilled with marijuana. [11]

Side Effects

The long-term side effects in a fully mature and developed person are not the same for an adolescent. In adolescents, the use of marijuana can lead to an abnormal brain shape, loss of IQ points, an increased chance of lung cancer, and even respiratory issues. Short-term side effects, such as anxiety, fear, and distortion in time perception may also take place, but these experiences are not universal. Because an adolescent does not have a fully developed brain, their ability to function correctly as an adult may be stymied compared to someone who does not use marijuana. [3]

Treatments

Current treatments for cannabis use disorders are limited. The majority of the treatments are supportive care, such as cognitive-behavioral therapy (CBT), motivational enhancement therapy (MET), and contingency management (CM). Sufficient evidence has proven that behavioral therapy can help those who seek treatment for marijuana use disorders. Unfortunately, the rate of improvement with behavioral therapy does not have a high “success” rate. Only 17-34% of adolescents who vouch for abstinence from marijuana in prior months self-reported no substance use in all behavioral treatments. Since these percentages are low, there is a lot of room for improvement in outpatient care. [8]

Conclusion

In 2019, 37% of American high school students reported using marijuana at some point in their lives, and 22% report using it in the last 30 days. Approximately 3 in 10 people have a marijuana use disorder. People are more prone to this disorder when they start frequently using marijuana at a young age [9]. There are many existing behavioral therapy treatments, but other alternatives in treatments should be available for a more positive outlook on brain development for adolescents.
The effects of marijuana at a young age can be severe to a child’s development and should be studied further for more accurate findings and treatments.

References


LSD vs. Heroin: Different Drugs with a Notorious Past
Donya Atashie

Abstract
LSD and heroin are two very different drugs: one is hallucinogenic, and the other is an opioid. However, they are connected by sudden eruptions of popularity and had public attention drawn to them. The Summer of Love in the 60's attracted many to LSD, and the present day opioid epidemic has led many to become addicted to heroin. While similar in their social impact, research on LSD is quite limited compared to that on heroin. More is known about heroin and what neural systems it affects due to this inequality in research funding. Differences also exist between the two drugs in their impacts on the brain, and in how the body reacts to each one. While LSD binds to serotonin (5-HT₂A) receptors, heroin binds to opioid receptors. Long-term effects also differ between the two, as well as the “addictiveness” and likelihood of experiencing withdrawal symptoms. Comparing the two here demonstrates that not many commonalities explain the two drugs creating similar reactions in the public response, and that they differ in most facets.

Introduction
The United States has had multiple large drug uprisings, causing mass chaos across the nation in short periods of time. From the LSD crisis in the 60's to the heroin epidemic of the current day, it seems that, although years apart, these two different drugs have created a similar chaotic reaction in the country, becoming the center of the media and causing mayhem amongst the general population. This paper will focus on these two chaos-inducing drugs (LSD and heroin) and their social, long term, physical, and neurological effects.

In recent years, there has been an opioid epidemic, including that of heroin. Opioid overdoses accounted for more than 40,000 deaths in 2016, and more than 70,000 deaths in 2019 [4]. This opioid epidemic has come in three waves: prescription opioids, heroin, and then fentanyl. The first wave (prescription opioids) began in the 1990s, when pharmaceutical companies began increasing the prescription of opioids (pain-relieving drugs), with the promise that addiction to these drugs was unlikely [4]. This was not accurate, and increased prescription of these opioids began the onset of the epidemic [5]. One outcome of this first wave was that 40% of opioid overdose
deaths in 2016 involved a prescription drug [4]. The second wave of the epidemic was the rise of heroin usage starting in the 2010s [5]. Between 2002 and 2013, the rate of heroin overdose deaths quadrupled, killing more than 8,000 people in 2013, and 14,480 between 2019-2020 [6]. The third wave (fentanyl/synthetic opioids) began in 2013, and included drugs like heroin, counterfeit pills, and cocaine [5]. While some state programs and individual means exist to help combat opioid addiction, more are needed to help prevent and stop the widespread usage of opioids [6].

In 1967, the hippie movement, or the “Summer of Love,” popularized the usage of LSD. Forming a counterculture, this was a movement in San Francisco, California, with many teens and youths fleeing to the city and taking any drugs available, including LSD [1]. This came after an era of large political and social tensions in the country, and the movement was intended to give people a “freer” life. LSD was said to be the “gateway to spiritual enlightenment” [1]. Being widely accessible, it quickly became apparent that the pleasant effects of LSD were highly desirable, and this was causing a public health crisis. Much of the LSD sold on the streets was highly dangerous and not pure, resulting in various harmful outcomes ranging from bad trips and psychosis to extreme cases of self mutilation [1]. In 1968, LSD became criminalized, causing some to believe that “the government effectively and quietly persecuted and silenced the hippies because of their untraditional way of living and thinking” [3]. LSD was evidently the pinnacle drug of the ‘60s, and a close parallel to heroin in the current era. This article will compare and contrast LSD and heroin effects similarities and differences in physical, neurological, societal, and long-term effects.

**Neurological effects**

Although these drugs are similar in their social responses and schedule of drug, there is a large contrast in their physical, neurological, and long-term effects. Differences exist in the pathways of the brain that they affect, and how the human body reacts to each one. However, while going through these comparisons, it is important to keep in mind that heroin is studied more than LSD and, thus, has a greater breadth of information available. Research articles on heroin vastly outnumber research articles on LSD after 1975; we can see in Figure 1 the number of papers published on LSD and heroin from 1950 to 2020.
When heroin enters the body, it binds to the opioid receptors in the brain’s cortex, which is linked to the reward system in the brain [7]. With this opioid receptor activation, a signaling cascade is initiated that leads to dopamine release, which causes the “high” that people experience [7]. A sudden rush of joy and happiness is experienced. The dependency that occurs is due to how pleasurable this sudden rush of positive feelings is. To understand the dependency, we must understand the reward system, and how opioids affect the brain. Humans naturally produce opioids to alleviate pain; opioid receptors exist in pain pathways throughout the body. However, the more unnatural and external opioids are absorbed, the fewer natural opioids the body produces, leading to dependence on drugs to achieve the same level of relief [7]. Since heroin leads to a greater release of dopamine than natural rewards, the brain becomes accustomed to this increased level, and no longer responds to the lesser dopamine release from natural reward sources such as food, sex, and socializing [9]. The reward system in the brain encourages people to repeat actions that lead to dopamine release, as this release informs the brain that this behavior or sensation is good for the person [9]. However, a reward system that is dependent on heroin is one that encourages the person to repeatedly use the drug [9]. This cycle of chasing dopamine release is the very nature of drug addiction.

On the other hand, LSD binds to serotonin receptors, indirectly affecting dopamine levels in the brain [13]. These serotonin (5-HT_{2A}) receptors are responsible for the hallucinogenic effects caused during an acid trip [13]. Through MRI sensory and cognitive processing, it has also been shown that visual processing is slowed down, which causes decreased amygdala activity [13]. This correlates with a decreased response within the brain to negative facial expressions [13]. Generally, brain activity increases in most regions following LSD intake, and creates a multitude of changes in brain connectivity [13]. However, many of them are not well understood due to a lack of research and studies on LSD. A recently discovered action of LSD shows continued effect on the brain, even after it is eliminated from the bloodstream. These long lasting effects of the drug can be explained due to a “lid” that is formed by the receptor over the LSD molecule [15]. A mere 100 micrograms of the drug can lead to effects lasting longer than 12 hours. This lid action is a process in which, once the LSD molecule binds to the serotonin receptor, a loop of protein forms a lid over top, trapping the LSD molecule in the receptor itself [15]. This hinders the release of the drug from the receptor into the brain, making the trip last for hours. A team researching LSD created a receptor without the ability to create this lid, and found that this would lead to very short acid trips. Nonetheless, humans do not have such receptors [15]. LSD and heroin have similarities and differences in how they impact the brain. These two drugs both impact dopamine levels in the brain. However, heroin directly affects and binds to the dopamine receptors, while LSD indirectly affects them.

**Physical Effects**

Physical effects of heroin are much different than those of acid. While the sudden surge of dopamine occurs, physical effects such as clouded thinking, dry mouth, nausea, vomiting, warm skin, and severe itching are also present [12]. The surge of dopamine and feeling of happiness only lasts a few minutes, and slowly wears off over the course of a few hours [18]. When one attempts to stop using after dependency has formed, severe withdrawal symptoms can occur, mimicking
symptoms of intense flu such as chills, nausea, and exhaustion, as well as a craving for more drugs [18].

An actual acid trip can last as long as 8-12 hours, although the distortion of time perception caused by the drug can make it seem much longer to the user [10]. During this trip, people can experience physical effects including sweating, increased heart rate and body temperature, and dehydration [10]. Sometimes the hallucinogenic effects of the drug can cause a mix up of sensory perceptions and lead to things like synesthesia, which is when senses are combined, such as hearing smells or seeing sounds [10]. Other effects can include dry mouth, reduced appetite, and dizziness. Furthermore, the effects of a “bad trip” can be much more severe and scary than those of a “good trip”. A bad trip can create a sense of psychosis, like being in a living nightmare, whereas a good trip can create a sense of peace and spiritual awakening [11].

**Long Term Effects**

Each of these drugs has varying long-term effects. Starting with heroin, the increasing numbers of heroin abusers in recent years resulted in abundant research regarding its long-term consequences. One of the most notable effects of heroin is the development of Alzheimer’s Disease [7]. Long-term heroin use can lead to inflammation in the brain which creates structural changes [7]. Furthermore, heroin can significantly deteriorate the brain’s white matter, which can cause difficulty making decisions and regulating behaviors [7]. The structural changes that occur within the brain can lead to decreased oxygen in the bloodstream, poor or worsened impulse control, and blood vessel problems [7]. Organ failure, lung infections, and stroke may also occur [18]. Sharing injection needles may lead to viral infections like HIV and hepatitis, and blot clots may form at injection sites [18].

In regards to LSD, one of the more severe long-term effects can be hallucinogen persisting perception disorder, or HPPD [16]. This is when the effects of a hallucinogenic drug last long after the drug has cleared from the body, and can last for days or even weeks [16]. This can include intense flashbacks, which can sometimes be pleasurable, but are more often distressing, and can lead to the development of more frequent flashbacks [17]. A thorough review of HPPD prevalence, etiology, and current research can be found in Martinotti et al., 2018 [19]. Short-term, pleasurable flashbacks may occur repeatedly following an acid trip and are not classified as HPPD. However, more long-lasting visual hallucinations have been officially recognized as HPPD by doctors, but have not been extensively researched due to the strong restrictions on studies about LSD [17]. Furthermore, a link may exist between long-term LSD use and the development of psychiatric disorders such as schizophrenia (although research is limited) [16]. The long-term effects of LSD are also seen in the elderly population nowadays [2]. Those who were young and in the main demographic of the Summer of Love in the 1960’s are now in their sixties and seventies. In a study conducted by Janice Hoffman et al. in 2010, it was found that the history of excessive LSD usage can amplify the health problems of elderly who had participated in the Summer of Love [2]. With this knowledge, it has become increasingly important for medical providers to clarify the history of drug use, even among their elderly patients [2].
### Comparison Table

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### Conclusion

These two Schedule I drugs are extremely different in most aspects, including their impacts on the brain, their physical and long-term effects, and also the amount of research available regarding each one. LSD is a hallucinogenic, not highly addictive drug potentially leading to psychosis-like symptoms. Heroin is an extremely addictive opioid that can damage the brain and alter the reward system; it can also cause severe withdrawal symptoms when one tries to stop usage. Although the drugs differ, they were both sensational in certain periods of time in the United States. The current opioid epidemic is due to a giant rise in the popularity of the drug, similar to LSD becoming a large spectacle in the 1960’s Summer of Love and Hippie movement. Although different, these two drugs have each had a similar notorious past, and caused chaos within the
References


Theory of Mind: The Human Brain & Artificial Intelligence

Shrivibha Lanka

Abstract

It's no doubt that the human brain is a mastermind at problem solving. The theory of mind helps us ‘predict’ the potential actions of our peers. Artificial intelligence is technology which can think like the human mind. The human brain has the ability to solve problems by using the theory of mind. But how is the theory of mind found in machinery that uses artificial intelligence? How is artificial intelligence able to predict and respond to us? Is artificial intelligence just replacing the human theory of mind?

What is the Theory of Mind?

Psychologically, the theory of mind otherwise known as ToM, is the cognitive theory which helps us understand others and problem solve. Theory of mind is when we are able to ‘predict’ our peers’ actions and able to predict their further emotions [1]. Theory of mind is our most helpful tool when it comes to problem solving and predicting, as it helps us determine our own actions based on others. The human theory of mind is a sort of segway to almost mindreading in a sense [1]. The theory of mind is associated with many regions in the brain such as the superior temporal gyrus, temporoparietal junction, medical prefrontal cortex, precuneus, and amygdala [2]. These parts of the brain help decode and process information.

What is Artificial Intelligence?

Artificial intelligence, also known as AI, is the “new big thing” in machinery, technology, and computers. Artificial intelligence is constantly expanding to fit our daily lives. It is a ‘mimicry of basic human responses’ [3]. The concept of artificial intelligence was first founded by Alex Turing back in the 1950’s[4]. Alex Turing performed his research to answer the question: “Can machines think?” His future discoveries were all based on understanding artificial intelligence. As the concept of artificial intelligence began to grow, many began to take interest in artificial intelligence such as the roles AI plays in US Department of Defense’s technology [3]. Today, artificial intelligence is a major part of our daily lives. artificial intelligence is found in many of our everyday objects such as telephones, home appliances, and cars.
How is Theory of Mind ‘seen’ in Machinery and Artificial Intelligence (Deep and Machine learning)?

Computers and machinery do not have brains, but with the use of artificial intelligence, they are able to learn. Just like humans have brains that can use the theory of mind to predict peers actions and emotions, Artificial intelligence has its own ways of predicting human-like responses which is far more different than how we interpret responses [1]. Computers do this through a process called cognitive computing, the crucial component of artificial intelligence that allows computers to mimic the human brain [4].

One of the many ways artificial intelligence computing devices learn, predict, and process information is through machine learning. Machine learning is when the computer/device is ‘fed’ information. After it is loaded with information, it can not only learn but infer with the given information to a certain extent without human help [5][6].

Deep learning (DL), on the other hand, is a more complex type of computer learning than machine learning because it has many more components to it. DL uses artificial neural networks to interpret and infer information [6]. DL is different from machine learning as deep learning is able to analyze data at a higher level since it is rooted with artificial neural network technology [5].

How does the Theory of Mind in the brain compare to Machine/Deep Learning in Artificial Intelligence?

The theory of mind in the human brain is very similar to how artificial intelligence uses machine/deep learning to interpret data. Both artificial intelligence and the theory of mind are used to infer and predict outcomes. The theory of mind in the human brain is used to predict human responses and actions, while machine/DL is used to interpret data in computers. DL uses artificial neural networks that mimic the human brain’s neural networks since they are both used for the sole purpose of analyzing information [6].

Is the Theory of Mind getting replaced by Artificial Intelligence?

Deep learning in artificial intelligence, as discussed previously, is like the virtual version of theory of mind. Theory of mind cannot get replaced virtually as it is our natural instinct in problem solving and is a very useful tool that helps us generate our decisions.
Artificial intelligence should have a limitation as it is very similar to the human mind and AI gets more powerful by obtaining more information over time. We should not let artificial intelligence make decisions for us as that can be dangerous. This actually happened in 2017 when Facebook made two artificially intelligent robots [8]. These two robots started communicating and eventually made their own language that no one but them could understand [8]. This proved how powerful artificial intelligence could be and how much potential it has. Robots or computing devices showing AI's power could be dangerous as AI could make technology more powerful than it currently is. The technology can grow very powerful as seen before with the Facebook example. Therefore, we should not allow artificial intelligence to replace the human theory of mind. If artificial intelligence does replace the human theory of mind, humans will not have the power to solve problems.

References


The%20term%20artificial&text=Early%20AI%20research%20in%20the%201960s%20%20aimed%20to%20mimic%20basic%20human%20reasoning.


Current and Emerging Treatment Options for Hepatic Encephalopathy: A Systematic Review and Meta-Analysis

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Abstract

Hepatic encephalopathy (HE) is a devastating consequence of liver failure that results in potentially debilitating cognitive impairment affecting patients and their caregivers alike. HE burdens both the patient and caregivers with substantial physical, emotional, and monetary costs, as well as health care systems with frequent hospitalizations. Understanding of the pathogenesis is limited, leading to the approval of few effective treatment modalities. Current standard of care treatments include non-absorbable disaccharides (NADs) and Rifaximin. Multiple other treatment modalities are gaining support as more data becomes available. Mechanisms of action for these investigational therapies include altering the gut microbiome. This is hypothesized to reduce the bacterial production of ammonia, increasing the availability of amino acids in the body, stimulating urea synthesis, decreasing inhibitory neurotransmission, and increasing elimination of ammonia. This article reviews and analyzes the mechanism of action, efficacy and safety of newer, non-traditional therapies for HE based on currently available clinical studies, as well as examines practical considerations and clinical positioning in treating patients with HE.

Introduction

Hepatic encephalopathy (HE) is a frequent complication of liver disease that affects patient morbidity, mortality, and quality of life, often resulting in increased caregiver burden. Overt HE will manifest in 30-40% of cirrhotic patients during their lifetimes [1]. Patients with cirrhosis and HE have a 2-fold increased rate of mortality over one year compared to cirrhotic patients without HE. It is also more costly to the health care system and to the families paying home caregivers, compared to other manifestations of cirrhosis, with 110,000 hospitalizations occurring from 2005-2009 [1]. Family member caregivers are often negatively affected given the significant time burden, which is usually coupled with detrimental emotional effects. The pathogenesis of HE is complex and poorly
understood, with many studies being underpowered or containing design flaws that make a further elucidation of the exact causes of HE difficult [1]. The presentation of HE is also varied and non-specific, making diagnosis and proper classification challenging (Figure 1). Currently, HE is classified by the type of underlying disease, time course, severity of manifestations, and precipitating factors [1]. Due to the unclear underlying pathogenesis and wide spectrum of presentation, data has been slow to emerge regarding potential treatment options beyond the standard of care. Current approved therapies focus on decreasing serum ammonia levels by reducing gut ammonia formation and absorption. Newer emerging therapies have been based on an increased understanding of HE pathogenesis - these therapies focus on reduction of ammonia through decreased absorption or increased elimination, replacing anabolic constituents such as amino acids that are decreased in cirrhotic patients with HE, altering the gut microbiome through various methods, or by decreasing the end result of inhibitory neurotransmission. This article is a systematic review and analysis of the most recent and pertinent literature that discuss the use of these novel therapies in treating HE.

1. Non-Absorbable Disaccharides

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<tr>
<th>WHC</th>
<th>Symptoms</th>
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<tr>
<td>Minimal</td>
<td>Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change</td>
<td>Nil</td>
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<td>Covert</td>
<td>Trivial lack of awareness</td>
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<td>Grade IV</td>
<td>Coma</td>
<td>Decerebrate posturing</td>
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Lactulose

Non-absorbable disaccharides (NADs), such as lactulose (beta-galactosidofructose) and lactitol (beta-galactosidosorbitol), have been mainstays of treatment of HE since first described by Johannes Bircher in 1966 [2]. NADs reduce the effect of ammonia in the induction of hepatic encephalopathy through multiple mechanisms. NADs are fermented in the colon, increasing intraluminal osmolality and reducing pH. Reducing the pH prevents the conversion of ammonium to ammonia. The increase in intraluminal osmolality results in a cathartic effect in the colon. It is also suspected that NADs affect the colonic microbiota beneficially.

A Cochrane review by Gluud et al., published in 2016, included 38 randomized controlled trials (RCTs) that investigated the treatment of hepatic encephalopathy using NADs [2]. There was a reduction in mortality in patients presenting with overt HE but not with minimal HE. Minimal HE can manifest as trivial lack of awareness, change in
sleep patterns, and lethargy. There were no differences in effect between lactulose and lactitol. Unfortunately, none of the included RCTs provided details on possible encephalopathy-precipitating factors which may impact the effect of NADs. Adverse events including liver failure, spontaneous bacterial peritonitis, hepatorenal syndrome, variceal bleeding were reduced as a whole. The direct cost/benefits of NAD treatment were not examined in the individual trials, but these substances were felt to be cost-effective. Lactulose is inexpensive, and any reduction in hospitalization duration or occurrence would reduce costs associated with HE. An RCT investigated the use of prophylactic lactulose in patients with cirrhosis who had never had an episode of overt HE. The treatment group was given lactulose while the control group was not. The investigators found that lactulose improved minimal hepatic encephalopathy in 66% of patients when measured by psychometry, figure connection test, digital symbol test, serial dot test, line tracing test, and critical flicker frequency testing at inclusion and three months [3]. Despite this finding, guidelines on hepatic encephalopathy do not recommend primary prophylaxis for prevention of overt HE except in patients with cirrhosis and a known high risk of developing HE [1]. Recommended dosing is 25mL of lactulose syrup every 1-2 hours until at least two soft or loose bowel movements per day are produced, with continued maintenance of dosing to maintain two to three loose bowel movements per day [1]. This treatment is FDA-approved. Use of lactulose can be limited in a clinical setting, as overuse can lead to dehydration, hypernatremia, perianal skin irritation, and aspiration. Underdosing of lactulose can also lead to breakthrough HE episodes.

II. Antibiotics

Rifaximin

Rifaximin is a broad-spectrum oral antibiotic with very low bioavailability and antibacterial activity primarily within the colon [4]. It acts on gram-positive and gram-negative aerobic and anaerobic bacteria and modifies the gut microbiome. It is suspected that subtle changes in the microbiome composition, in regards to Lactobacillus, Streptococcus, and Veillonella, may affect ammonia production and endotoxin release [4]. A favorable microbiome is also suspected to lower the proinflammatory state of the liver by increasing intestinal epithelial homeostasis [4]. A systematic review by Kimer et al. from 2014 analyzed 19 RCTs, including a total of 1370 patients, and found that Rifaximin had a beneficial effect on secondary prevention of HE with increased rates of full resolution when compared to control groups including placebo, other antibiotics such as neomycin, and other disaccharides [5]. Rifaximin also increased the proportion of patients who recovered from HE and reduced mortality [5]. Although the included studies showed no clear benefit of Rifaximin, the number of patients was small and it was difficult to make definitive conclusions. Multiple studies have shown the effectiveness of adding Rifaximin to lactulose for prevention of recurrent HE. Another single-center, retrospective study investigated HE recurrence with Rifaximin 600mg BID plus lactulose versus lactulose alone with median follow up 18 months. The rate of HE recurrence was 15.9% for the Rifaximin plus lactulose group versus 33.3% for the lactulose monotherapy group [6]. The current guidelines recommend Rifaximin as an effective add-on therapy to lactulose to prevent an overt HE recurrence [1]. Rifaximin is also an FDA approved treatment.
Neomycin

Neomycin is another widely used treatment for HE. It acts to inhibit glutaminase, which, in turn, decreases ammonia synthesis from glutamine in the intestine [7]. Although historically, it has been widely used, there remains a lack of data supporting its efficacy in comparison to current first-line therapies. The most recent study from Strauss et al. in 1992 compared 20 patients treated with 6g neomycin daily versus 19 with placebo, and found that the time elapsed between the initiation of the medication and regression to grade zero HE was 39.11+/−23.04 hours for neomycin versus 49.47+/−21.92 for the placebo group, and this did not reach statistical significance [8]. Orlandi et al. compared neomycin to lactulose in an RCT with 173 total patients. Neomycin 1g four times daily with 30-60g magnesium sulfate purgation were given orally to patients with grade I HE. Neomycin 2g four times daily with 30-60g magnesium sulfate were given to patients with grade 2 or 3 HE. The lactulose group was treated with 10-35ml of 50% lactulose syrup orally three times daily. Both groups were treated for 14 days and there was no significant difference between the treatments in regards to improvement in mental status, asterixis score, or ammonia levels. A limitation of this study was that the grading of HE was not standardized compared to more modern trials [9].

Long-term use of neomycin can result in neuro and nephrotoxicity. Guidelines state that neomycin has its advocates and can be considered as an alternative choice to treat overt HE [1]. Neomycin is FDA-approved for the treatment of overt HE.

Metronidazole

Metronidazole has been studied as a potential treatment for overt HE. The mechanism of action involves metronidazole’s activity against anaerobic gut flora that have urease activity and convert urea to ammonia, thereby reducing serum ammonia levels [7]. In one study, 11 patients with mild to moderate HE and 7 with severe HE were treated with neomycin 1g qd or metronidazole 0.2g qid for one week, with assessment of mental status scores at the end of treatment [10]. Both the mild/moderate and severe HE groups showed improvement in mental status scores and a decrease in astersixis with both drugs. Mean arterial ammonia levels before and after treatment did not show a significant difference. The authors concluded that metronidazole may be just as effective as neomycin in treating overt HE [10]. Long-term use has been limited by concerns of neurotoxicity, including peripheral neuropathy and ototoxicity, and nephrotoxicity [11]. An open label study by Mekky et al., in 2018 included 120 patients randomized to Rifaximin or metronidazole therapy for treatment of an acute episode of overt HE [12]. The number of patients who showed clinical improvement was not statistically different between treatment groups and hospitalization duration was comparable with 4.2+/−2.1 days versus 3.9+/−1.7 days for the metronidazole and Rifaximin groups, respectively. This data was obtained at the end of the treatment duration. There was no significant difference in ammonia levels from baseline in either treatment arm (160.77+/−185.mcg/dL versus 207.95+/−218.mcg/dL) in the metronidazole and Rifaximin groups, respectively. The authors concluded that these therapies were similar in efficacy [12]. Lactulose was not compared in this study. Guidelines note that the data is not strong enough to warrant use of metronidazole as maintenance therapy over Rifaximin, given the potential side effects, but that it is an alternative option for the treatment of overt HE [1]. Metronidazole is not FDA-approved for the treatment of HE.
Vancomycin

In addition to the well-established use of vancomycin to treat Gram-positive bacteria, it also reduces the burden of Gram-negative anaerobic rods in the stool, which in turn decreases the amount of urease available to produce ammonia [7]. The mechanism of action is similar to metronidazole in this regard. The data on vancomycin’s role in HE treatment is sparse. Tarao et al. published a double blind crossover trial in which 12 patients underwent a two week course of lactulose with titration to 2-4 bowel movements per day and then all were given vancomycin 2g qd for 8 weeks, after which 6 patients discontinued vancomycin and started lactulose while the other 6 were continued on vancomycin for another 8 weeks [13]. The groups then switched medications for another 8 weeks. After this, mental status was assessed. The grade of HE went from 2 to 0 in vancomycin-treated patients and resolution of HE occurred more quickly with vancomycin than with lactulose. This study was limited by the small number of participants and no clear delineation of the grade of improvement with lactulose. There is very little published data on the use of vancomycin, and for this reason, it is not widely used to treat HE. The guidelines do not mention vancomycin as a treatment for HE [1]. It is not FDA-approved for this indication.

III. Alternative Therapies

Branched Chain Amino Acids

Branched-chain amino acids (BCAAs) have been investigated as a potential treatment for hepatic encephalopathy, but data is very limited and there are no strong trials available. Cirrhotic patients have a general deficiency of circulating amino acids compared to healthy controls as a result of nutritional derangements, and have excess muscle catabolism. This has been documented in prior studies. Skeletal muscle plays an important role in serum ammonia reduction. BCAAs have been postulated to reduce malnutrition and consequent reduction in muscle mass, thereby improving ammonia metabolism [14]. One Cochrane review identified 16 RCTs with 827 participants with cirrhosis treated with BCAAs vs other interventions including no intervention, NADs, antibiotics, or diet. There was no difference in mortality between the BCAA intervention group and the other interventions treated as a group [14]. BCAAs were associated with a beneficial effect on HE compared to controls consisting of placebo, diets, lactulose, or neomycin. The benefit was only noted when excluding trials with a lactulose or neomycin control group. Guidelines recommend oral BCAAs as an alternative or additional agent to treat patients who are nonresponsive to conventional therapy [1].

L-ornithine L-aspartate

L-ornithine L-aspartate (LOLA) acts to enhance ammonia detoxification by stimulating urea synthesis in hepatocytes [15]. Ammonia removal by skeletal muscle is also stimulated by LOLA via the promotion of ammonia incorporation with glutamate to form glutamine [15]. One systematic review of LOLA’s role in HE treatment included 8 RCTs with 646 patients with cirrhosis and compared LOLA to placebo, lactulose, or probiotics. It demonstrated LOLA was more effective than placebo and equally as effective as lactulose or probiotics for improvement of overt HE and minimal
A systematic review and meta-analysis of 15 RCTs with 1023 patients showed the benefit of LOLA in acute or chronic episodes of HE but not in minimal HE when compared with placebo, but the body of evidence was small [17]. A subsequent review and meta-analysis pooled data from nine trials assessing the effects of LOLA on mental state improvement, and showed significant benefit with improvement occurring more often using the West Haven criteria (RR=1.36 and 95% CI 1.10-1.69) and by psychometric testing (RR=2.15 and 95% CI 1.48-3.14) [18]. A head-to-head trial by Poo et al. comparing LOLA to lactulose has shown that LOLA is at least equivalent to lactulose in lowering serum ammonia but provided greater improvement in mental state and number connection test scores [19]. Although LOLA is not available in the US, guidelines suggest IV LOLA can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy [1]. It is not FDA-approved.

**Albumin**

In cirrhosis, oxidative stress, inflammation, and the susceptibility to bacterial infection can play a role in decompensation and the development of HE. For this reason, substances that reduce oxidative stress and inflammation may have a beneficial effect. Albumin has been shown to reduce oxidative stress and vasodilation and increase oncotic pressure. Published studies, however, have shown inconsistent benefit from the use of IV albumin. A meta-analysis recently investigated the role of albumin in the prevention of HE [20]. In this meta-analysis, 6 studies with 889 patients suggested that, while albumin infusion may reduce risk of overt HE in cirrhosis, the difference was not statistically significant when compared to a control without albumin infusion. Sharma et al. investigated albumin plus lactulose versus lactulose alone with the primary endpoint being complete reversal of HE [21]. In this RCT, 120 patients were randomized evenly to lactulose plus albumin or standard therapy with lactulose. 75% of patients in the combination group versus 53.3% of the patients in the monotherapy group had complete reversal of HE. Mortality was also lower (18.3% versus 31.6%, respectively). There were also significant decreases in arterial ammonia, IL-6, IL-18, TNF-alpha, and endotoxins, with greater decreases in the combination group. A recently published study in 2021 by China, et al. randomized decompensated, hospitalized cirrhotic patients with a serum albumin level of less than 30g/L to receive either a 20% albumin solution with median 200g albumin per patient for up to 14 days or until discharge, or standard care with median 20g albumin per patient [22]. Primary endpoints were new infection, kidney dysfunction, or death between 3 and 15 days after initiation of treatment. 777 patients underwent randomization. The primary end points did not show significant difference between the groups and, the rates of encephalopathy were not appreciably different. Given these disparate findings of efficacy, the guidelines do not recommend albumin infusions for the purposes of HE prevention or treatment [1].

**AST-120**

AST-120 is a carbon microsphere adsorbent that was initially approved in Japan in 1991 in order to delay the initiation of dialysis in uremic patients [23]. AST-120 has been shown to reduce oxidative stress and arterial ammonia in rat models by binding to ammonia in the lumen of the gastrointestinal tract and allowing it to be passed from the GI tract [24]. The ASTUTE trial by Bajaj et al. examined the effect of AST-120 on covert HE [25]. This was a multi-center, double-blind, randomized, placebo-controlled trial with cirrhosis patients with covert HE. The patients were
randomized to 12g, 6g, or placebo daily for 8 weeks. There was no change noted at weeks 4 and 8, with a strong learning effect between screening and pre-randomization which confounded results. Ammonia levels were decreased from baseline in treatment groups but increased in placebo groups. Due to the lack of robust results, more research is felt to be needed and guidelines do not recommend AST-120 as a treatment for HE [1].

**Acetyl-L-carnitine**

It is hypothesized that acetyl-L-carnitine may benefit HE by increasing urea genesis and decreasing blood and brain ammonia [26]. It also is hypothesized that acetyl-L-carnitine facilitates uptake of acetyl-coenzyme A in brain mitochondria which ultimately stimulates protein synthesis and prevents neuronal death. In 2019 a Cochrane review of five studies investigating this treatment and its role in treating HE was performed [27]. It included 5 Italian studies with a total of 398 patients. No trial in the review reported on rates of all-cause mortality or serious adverse events. Certainty of estimates regarding the effect on quality of life and mental/physical fatigue was low. There was very low quality evidence that blood ammonia levels were reduced but HE was not graded according to a standardized criteria. These studies were felt to be underpowered, with a high risk of bias. More robust studies are needed to validate the use of acetyl-L-carnitine in HE. Guidelines do not recommend the use of acetyl-L carnitine given paucity of data [1].

**Glycerol Phenylbutyrate**

Glycerol phenylbutyrate (GPB) is a tasteless liquid compound that removes nitrogen from the body in the form of urinary phenylacetylglutamine via an alternative pathway for ammonia waste. It is termed an ammonia scavenger. It has primarily been used to treat inherited disorders of hyperammonemia [28]. A multi-center, randomized, placebo-controlled trial to assess the ability of GPB, administered 6mL BID for 16 weeks, to decrease the incidence of HE events in cirrhotic patients who had at least two HE episodes [28]. One hundred seventy-eight patients were enrolled in total. Thirty-six percent of patients taking placebo had an HE event versus 21% in the GPB group. Time to the first event was longer, total events were fewer (35 versus 57), and HE hospitalizations were fewer (13 versus 25) in the GPB treatment arm, compared to placebo groups. Plasma ammonia levels were lower in patients on GPB. A limitation of this study is the low number of enrolled patients, and larger RCTs would be needed in the future to validate these results. Guidelines do not specify using GPB but are awaiting further clinical studies for an official recommendation [1].

**Flumazenil**

In HE, the balance of neurotransmission is predominantly inhibitory due to the effect of hyperammonemia [29]. HE patients are considered to have increased activity of GABA, which is the main inhibitory neurotransmitter in the brain, and may be amenable to GABA/benzodiazepine antagonism. Flumazenil competitively binds to the benzodiazepine receptor sites and may modulate inhibitory neurotransmission in this manner [29]. Goh et al. conducted a Cochrane Review in 2017 which included 10 RCTs and 842 participants with an acute episode of overt HE [30]. All RCTs
compared IV flumazenil with placebo, with daily dose of flumazenil ranging from 0.2mg to 6.5mg, with total dose between 0.2mg and 19.5mg, and with duration of treatment ranging from 10 minutes to 72 hours. Flumazenil was associated with a beneficial effect on HE. The beneficial effects were heterogeneous among the studies with improvement noted on EEG, subjective alertness, Number Connection Test, or Simple Reaction Time test. The benefit on HE was felt to be short-term, yet there were few adverse effects. Overall evidence supporting use of flumazenil for treatment of HE was felt to be low.

**Polyethylene Glycol**

Polyethylene glycol (PEG) is postulated to work in ameliorating HE due to it being highly effective as an osmotic laxative to facilitate the removal of fecal nitrogen [31]. Hoilat et al. published a systematic review and meta-analysis to investigate the utility of PEG in comparison to lactulose [31]. The review examined four RCTs with a total of 229 patients. The studies utilized the HE Scoring Algorithm (HESA) using both subjective and objective indicators, to gauge the effect of PEG versus lactulose on HE. Two RCTs with a total of 98 patients demonstrated a lower average HESA score at 24 hours post treatment in the PEG group compared to the lactulose group. Of these patients, there was also a higher proportion of patients who had a reduction of HESA score by greater than or equal to 1 at 24 hours post-treatment in the PEG group. Two RCTs showed a higher proportion of patients had a HESA score of 0 at 24 hours in the PEG group. There was no difference between groups in regards to hospital length of stay. This meta-analysis did not include studies that utilized a treatment arm with both PEG and lactulose. An RCT by Ahmed et al. compared PEG plus lactulose to lactulose alone in regards to HE resolution [32]. Twenty-nine patients were randomized to the dual treatment arm and 31 to lactulose monotherapy. There was a shorter median time to HE resolution in the dual therapy arm. Adverse events included mainly diarrhea. There was also improved survival at 28 days with the dual therapy arm but the difference was not statistically different at 90 days.

**Fecal Transplantation**

It has been shown that cirrhotic patients with HE have a gut microbiome with a reduced amount of beneficial species, such as Lachnospiraceae and Ruminococcaceae, with increased amounts of pathogenic species such as Enterobacteriaceae [33][34]. This has been postulated to increase systemic inflammation, which in turn can lead to deficits in cognition. Bajaj et al. in 2017 performed an open-label RCT where 20 patients with recurrent HE were randomized to receive fecal transplantation (FMT) from a donor with high amounts of Lachnospiraceae and Ruminococcaceae versus standard of care (SOC) with lactulose and Rifaximin alone [35]. The primary outcome was serious adverse events with secondary outcomes including changes in cognitive function at day 20, and changes in microbiota composition. 80% of SOC participants had adverse events, as compared to 20% of FMT participants, in whom the adverse events were felt to be FMT unrelated. Events that occurred in the SOC arm include pneumonia, chest pain, portal vein thrombus, anemia, gastroenteritis, and variceal bleeding. Five SOC and zero FMT participants developed recurrent HE during the follow-up period of 150 days. A secondary outcome was an improvement in cognition. There was a relative increase in beneficial microbials post-FMT relative to patients on SOC.
Limitations of this study were small sample size and the lack of a placebo arm. Bajaj et al. subsequently conducted another RCT on a group of 15 patients with HE randomized to FMT capsules or lactulose/Rifaximin [36]. Post-FMT microbial diversity was increased, with higher levels of Ruminococcaceae and Bifidobacteriaceae with lower Streptococcaceae and Veillonellaceae. Reduction in Veillonellaceae was also noted in post-FMT patients. There was a reduction in markers of inflammation, including interleukin-6 and serum LBP in the FMT group. This proved that FMT increased beneficial micobials and decreased pathogenic strains, although no clinical endpoints were assessed in this study.

Probiotics

As noted above, the gut microbiota in patients with liver disease has been shown to be altered to include more pathogenic strains. It has been theorized that probiotics may reduce harmful ammonia-producing bacteria, decrease ammonia absorption by decreasing pH, and decrease intestinal permeability [37]. A Cochrane Review by Dalal et al. in 2017 analyzed 21 trials with 1420 participants comparing probiotics with placebo or lactulose. The most commonly used probiotic product was VSL#3 [37]. When compared to placebo, there was no effect on all-cause mortality with probiotics, however, failure to improve HE score was lower, adverse events were lower, and plasma ammonia concentration was lower. The efficacy data on these items when probiotics were compared to lactulose was unclear due to low quality of evidence. The authors concluded that there was a high risk of bias and random error with overall low quality of evidence. Probiotics may be considered over no treatment, given their overall safety, although a clear therapeutic benefit has not been established. High-quality RCTs are needed to further investigate the role of probiotics in HE. Guidelines do not specifically recommend probiotic use but they do not recommend against it [1].

Diet

Malnutrition is a common complication of cirrhosis and is associated with muscle wasting. The loss of skeletal muscle prevents adequate removal of circulating ammonia and contributes to worsening encephalopathy [38]. This was demonstrated in a study by Nardelli et al. in 2019, which investigated the relationship between skeletal muscle mass and composition and the risk of progression from minimal to overt HE [38]. Sixty-four patients with cirrhosis had computed tomography to analyze skeletal muscle index. Skeletal muscle index was determined using CT to calculate the L3 muscle Hounsfield units (HU) to determine if it was consistent with known ranges for skeletal muscle or if it represented sarcopenia. They found that alteration in muscle composition (myosteatosis) (62.5% versus 12.5%) and sarcopenia (84% versus 31%) were more frequent in patients who had minimal HE versus no HE. The development of overt HE was independently associated with myosteatosis and sarcopenia. The rationale for this is that skeletal muscle acts to detoxify and metabolize ammonia. A reduction in skeletal muscle results in a reduction in ammonia clearance. Cirrhotic patients have increased resting energy expenditure, due to reductions in hepatic glycogen. As a result, there is increased use of amino acids, which must be offset by daily intake of 1.2-1.5g protein/kg body weight to maintain nitrogen balance [40]. Daily energy intake should be 35-40kcal/kg body weight. Fasting for longer than 3-6 hours should be avoided by eating small, frequent meals.
throughout the day, including a protein-based bedtime snack. The authors did not identify any high quality studies demonstrating the impact of diet intervention on hepatic encephalopathy.

**Conclusion**

The standard of care in treating hepatic encephalopathy has been non-absorbable disaccharides and Rifaximin. Still, there are newer therapies that are emerging that seek to modify multiple targets in the complex pathogenesis pathway leading to hepatic encephalopathy. Many of these therapies are supported by non-robust data but some have increasing support in the literature. This support may continue to grow as we better understand the underlying factors precipitating hepatic encephalopathy. Moving forward, larger clinical trials with robust methodology will be needed to support the addition of these therapeutic options to the treatment of hepatic encephalopathy.

**Acknowledgements**

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**References**


[16] Bai M, Yang Z, Qi X, Fan D, Han G. L-Ornithine L-aspartate for hepatic encephalopathy in patients with cirrhosis: a


Phase 1, Randomized, Placebo-Controlled Trial. November 2019;70(5):1690-1703.


Naegleria fowleri: The Brain-Eating Amoeba

Ginger Z. Watzinger

Abstract
With only 381 reported cases since 1937, it is safe to say that primary amoebic meningoencephalitis (PAM) is a rare disease. Perhaps precisely due to this rarity, little is known about the molecular mechanisms by which the microorganism Naegleria fowleri causes this fatal inflammation of the central nervous system in humans. This article provides an overview of what is known about the organism N. fowleri and the infectious disease that it causes in humans (PAM). Moreover, past cases of successful and unsuccessful treatment of PAM are analyzed, concluding that early diagnosis, a combination of antimicrobial drugs, and intracranial pressure management are crucial to curing patients of PAM. In addition, it is discussed why more research is necessary to shed light on the role of amoebic acetylcholine receptors in the treatment of PAM.

The Amoeba N. fowleri

The first section of the article is dedicated to N. fowleri as an organism. Commonly known as the brain-eating amoeba, N. fowleri is a bacteria-eating microorganism usually found in natural or artificial warm waters, such as warm lakes, hot springs, insufficiently chlorinated swimming pools, tap water pipes, or soil [1][2]. As a thermophilic amoeba, N. fowleri can survive in environments with a temperature of up to 46° C (115 Fahrenheit) with its optimal reproductive temperature at 42° C [3]. Despite this impressive adaptation to elevated temperatures, N. fowleri cannot survive in salt waters, such as the ocean [4].

N. fowleri can exist in three different lifecycle stages: (bi-)flagellate, trophozoite, and cyst [4][3]. For humans, it is the trophozoite stage that is pathogenic and infectious, even though the flagellate stage can be found in cerebrospinal fluid [3]. In the cyst stage, N. fowleri is resistant to suboptimal environmental conditions,
such as low temperature, or food scarcity [4][5]. Upon the termination of adverse environmental conditions, the amoeba can change into the trophozoite stage by releasing its spores through a small hole (ostiole) in the single-layered cell wall of the cyst; the cyst stage is not found in humans [6]. During the pathogenic trophozoite stage, N. fowleri is actively feeding (phagocytosis) and dividing via binary fission [3]. Binary fission is a mode of bacterial reproduction in which the parental cell duplicates its genetic material and then divides into two identical daughter cells [7]. Finally, in the flagellate stage, N. fowleri has two flagella which allow them to move through their environment [8]. While this flagellate stage is not infectious for humans, it can exist in the cerebrospinal fluid of humans, making the presence of flagellate N. fowleri a potential diagnostic marker for PAM [3][8]. More on the diagnosis and treatment of PAM is discussed later.

**N. fowleri causes primary amoebic meningoencephalitis (PAM)**

When water containing N. fowleri enters the nose of a human sufficiently high to reach the nasal cavity, N. fowleri causes an often-lethal infectious disease of the brain known as primary amoebic meningoencephalitis (PAM) [9]. Despite the high mortality of >95%, the symptoms of PAM usually begin only five to nine days after N. fowleri has infected the host [8][10]. The following section explains what happens to the nervous system of the host during this incubation time.

Shortly after N. fowleri has entered the nasal cavity of the host, they attach to the olfactory epithelium [11]. This is a mucous membrane that lines the inside of the nose and nasal cavity in humans [11]. In theory, like most epithelial cells, one of the responsibilities of the olfactory epithelium is to identify and eliminate pathogens by using immune cells, thereby preventing pathogens from further entering the host’s body [11]. Unfortunately, however, N. fowleri has evolved effective mechanisms to elude the responses of human immune cells [11]. In addition, some of the host’s well-intentioned immune responses may even cause further damage to the host’s nervous system due to inflammation [9]. This issue will be revisited later.

In the olfactory epithelium, N. fowleri begins digesting the astrocytes (neural support cells) and neurons of local nerve tissue. To do this, N. fowleri develops so-called food cups (Figure 2) which
allow them to easily digest large chunks of neurons and astrocytes via phagocytosis [12]. The damage thus caused elicits a further, increased immune response in the host, with various kinds of immune cells, including eosinophils, neutrophils, and microglia, acting at the site of nerve damage [13]. While the host’s immune system attacks *N. fowleri*, by, for example, engulfing them via macrophages, cytokines (chemical messengers used by cells) are released that cause inflammation [13]. During inflammation, the blood plasma inside local arterioles and venules is drained into the affected nerve tissue, delivering more immune cells and cytokines to the site of acute infection [14]. Despite these extensive host immune responses, *N. fowleri* usually successfully bypasses the central nervous system immune barriers and continues to travel to the host’s brain [8][13].

Specifically, *N. fowleri* travels along the cribriform plate [8]. This bone is located beneath the brain, connecting the olfactory bulb and the olfactory epithelium [15]. While traveling towards the host’s brain along this route, *N. fowleri* feeds on more astrocytes and neurons, while dividing constantly at an increased rate [8][16]. After a minimum of five days, the tissue damage caused by *N. fowleri* thus far leads to the first general symptoms in the host, usually taking the form of headache, fever, and later on a loss of sense of smell or taste [10][17].

While little is known about why *N. fowleri* prefers to travel via the cribriform plate, a scientifically plausible hypothesis relates to the neurotransmitter acetylcholine (chemical messengers used by neurons to propagate action potentials). It is known that the genome of *N. fowleri* contains a gene that is functionally similar to, i.e. a homolog of, the human gene mAChR1 (muscarinic acetylcholine receptor M1) which encodes one receptor protein subtype upon which acetylcholine acts to elicit a cellular response (Figure 3) [8][16][18]. The presence of an acetylcholine receptor would enable *N. fowleri* to detect the neurotransmitter in the nerve tissue of the human olfactory epithelium and olfactory bulb [8][16]. As a result, *N. fowleri* could follow the path of acetylcholine molecules towards the brain.

Once *N. fowleri* reaches the central nervous system of the host, substantial damage to nerve tissue in the olfactory epithelium and olfactory bulb has been caused (see figure 4). This leads to the onset of more PAM-specific symptoms such as loss of consciousness, altered mental state, or even coma [19]. One of the reasons why PAM is so lethal is linked to the rather late onset of these alarming symptoms. Usually, when patients seek medical attention, *N. fowleri* has already irreversibly damaged the host’s nervous system to the extent that curative treatment is impossible [10]. Crucially, what often ultimately leads to the patient’s death is the inflammation of the brain.
As more and more immune cells are recruited to the affected nerve tissue in the brain, more blood plasma is drained into the brain [14][20]. This is problematic because the brain is surrounded by skull bones, which means there is no possibility for the brain to expand across a larger space in response to the increased volume. As a result, the pressure on the brain (intracranial pressure) dramatically increases [8][20]. This elevated intracranial pressure is among the key symptoms of PAM that contribute to its fatality as a disease since vital nerves are pressed against the skull, making them dysfunctional [8][20]. The next section reviews two recently reported cases of PAM, focusing on the crucial differences between unsuccessful and successful treatment of PAM patients.

**Approaches to treatment of PAM**

As previously mentioned, PAM is a highly lethal disease, with an average mortality rate of >95% even when treated [20]. Despite modern molecular and microbiological treatments, no PAM-specific treatment or drug is currently available [10]. Usually, upon diagnosis of PAM, patients are treated with general antimicrobial and antifungal drugs such as amphotericin B [20]. This antifungal drug can bind to ergosterol, an organic compound (sterol) that is found in the cell membranes of *N. fowleri* [21]. As a result, holes form in *N. fowleri*’s cell membrane, leading to the leakage of essential ions such as K⁺, Na⁺, H⁺, Cl⁻ [21]. Ultimately, this leads to the death of *N. fowleri* cells, as they can no longer perform basic cellular metabolism.

An issue with amphotericin B as a treatment of PAM is that it is not specific to *N. fowleri* as a target organism. However, of far greater concern about the use of amphotericin B in human hosts is its ability to bind to the human sterol cholesterol, which is found in virtually all human cell membranes [22]. By damaging host cells as well as *N. fowleri* pathogenic cells, amphotericin B may have lethal effects for the host [22].

Even though currently available drugs against PAM are ineffective (contributing to its high mortality rate in humans), it is often the late detection and diagnosis of the disease that determines the survival of a patient [23]. It is challenging to diagnose PAM early on in the course of disease because afflicted individuals often do not experience alarming symptoms until towards the end disease stages [23]. This is the case because the inflammation of the central nervous system, that is, the excessive flooding of the host’s brain with pro-inflammatory cytokines, hyperactive immune cells, and blood plasma, takes place only after *N. fowleri* has reached and damaged the host’s central nervous system [10]. Thus, while nerve tissue damage in the olfactory epithelium caused by *N. fowleri* often leads to headache or fever, these symptoms are not alarming or specific enough to prompt medical professionals to consider *N. fowleri* when a patient seeks medical attention.

Nevertheless, in the later stages of the disease, some medical professionals ultimately do inquire whether *N. fowleri* is present in the host. In the case of such a suspicion, to diagnose *N. fowleri*-caused PAM beyond any doubt, some of the patient’s cerebrospinal fluid needs to be extracted to search for potential flagellate *N. fowleri* individuals, which would indicate an infection [20][23]. In the event that such flagellate *N. fowleri* are detected, a molecular confirmation using polymerase chain reaction (PCR) is necessary to verify that *N. fowleri* is present [23].
During PCR, the DNA of flagellate *N. fowleri* is amplified, i.e. multiple copies of it are obtained, and then compared to the known DNA sequences of *N. fowleri*. The issue is that a PCR diagnosis takes time, which is crucial for the effective treatment of PAM [23].

For example, in 2021, a case of PAM in an 18-year-old male in Turkey resulted in death because the patient sought medical attention only seven days after the initial infection [23]. Tragically, after medical professionals and scientists had confirmed the presence of *N. fowleri* in the patient, further treatment remained ineffective, as the inflammation of the central nervous system had progressed beyond reversibility [23]. This case illustrates how important a rapid diagnosis and early treatment for curing patients with PAM are. An earlier diagnosis would likely have saved the patient’s life.

Despite the challenging diagnostic procedure of PAM and the high lethality, there are instances of successful treatment. Such successes are usually the result of a combination of factors, which will be elaborated on further. In 2013, for example, medical professionals and scientists in the USA were able to cure a 12-year-old female who suffered from PAM [20]. The first factor that contributed to the successful treatment was early diagnosis. The patient sought medical attention three days after the initial infection, reporting symptoms such as headache, fever, and nausea [20]. While the initial neurological scan of the patient’s brain was unsuspicious, the extraction and analysis of cerebrospinal fluid revealed the presence of *N. fowleri*, which was then further confirmed via PCR [20].

Consistent with the presence of *N. fowleri* and the diagnosis of PAM, an scan of the patient’s brain showed damage (hemorrhages and lesions) in left frontal lobe (see figure 4) [20]. These lesions and hemorrhages are the result of *N. fowleri* digesting neurons astrocytes in the left frontal lobe of the patient’s brain. Fortunately, six months after the initial infection, the patient had recovered completely, with no long-term consequences or nerve tissue damage [20].

To combat the *N. fowleri* in the host’s nervous system, a combination of antimicrobial and antifungal drugs, including amphotericin B and Miltefosine, was used as a treatment [20]. More specifically, initially the patient received amphotericin B at a higher and then lower dose, then Azithromycin, Fluconazole, and Rifampin were administered. Finally, a daily dose of Miltefosine was given [20]. The use of these various, different antimicrobial and antifungal drugs is the second factor that allowed the medical professionals to successfully treat the patient. This is the case because rather than relying on the effects of one drug, such as amphotericin B which can also be
cytotoxic to the host’s cells, the combined effectiveness of drugs with different targets was employed [20][22].

The third and final factor that contributed to the patient’s survival of PAM was how the inflammation-induced internal pressure on the brain (intracranial pressure) was managed. Drawing on techniques from traumatic brain injury treatment, the medical professionals reduced the fatal, elevated intracranial pressure on the patient’s brain (50 mmHg) by draining some of her cerebrospinal fluid and inducing hypothermia (32-34°C) [20]. The goal here was to reach an intracranial pressure of about 20-30 mmHg. An improvement of the intracranial pressure-related symptoms was achieved two weeks after the onset of treatment [20].

Upon comparing the successful and unsuccessful treatment of a case of PAM in two young, otherwise healthy individuals, it becomes clear that early diagnosis of PAM is a key factor for survival. However, due to the delayed onset of symptoms (between five and nine days) and the rapid deterioration of the patient’s health thereafter, medical professionals often fail to detect N. fowleri on time [10][23]. The relatively slow diagnostic process involving neurological exams of the patient’s brain, cerebrospinal fluid extraction, and PCR confirmation of the presence of N. fowleri further contribute to delayed diagnosis of PAM. Nevertheless, as the 2013 case of PAM in a 12-year-old female demonstrates, an early diagnosis and treatment of PAM, using an array of antimicrobial and antifungal drugs as well as intracranial pressure management can lead to the survival of a patient [20]. This success provides evidence that with further research into the molecular mechanisms of disease, PAM may ultimately become a less fatal, treatable disease.

**Conclusion**

This article has provided an overview of N. fowleri as an organism and its interaction with the human nervous system as a pathogen, causing the rare, often-lethal disease PAM [5]. Even though there are, albeit few, reported cases of successful treatment of PAM, the mechanisms by which N. fowleri interacts with and digests the astrocytes and neurons of the host’s olfactory epithelium, olfactory bulb, and ultimately central nervous system, are poorly understood. A hypothesis centered around the human neurotransmitter acetylcholine exists [16][18].

To further our understanding of PAM as a disease, it is necessary to investigate N. fowleri as an organism. Specifically, the presence of a homolog of the human mAChR1 gene, which encodes an acetylcholine receptor, in N. fowleri’s genome may be a path worth researching. Present on many neuron cell membranes, the acetylcholine receptor interacts with the neurotransmitter acetylcholine as a ligand, allowing for the depolarization of the neuron’s cell membrane, i.e. the propagation of an action potential (Figure 3) [16][18]. Should N. fowleri possess a similar receptor that can bind with acetylcholine, it would be able to recognize acetylcholine in its environment and follow its path towards the human central nervous system, where acetylcholine is present at elevated levels [16]. Further scientific inquiry and controlled experiments will be necessary to shed light on the relationship between the N. fowleri homolog of mAChR1, the neurotransmitter acetylcholine, and ultimately, the treatment of PAM.
References


Sigma-1 Receptors: Promising Therapeutic Target for Alzheimer’s Disease

Aleena Kuriakose

Abstract

Sigma-1 receptors are one of two sigma receptor subtypes and are multifunctional ligands present in the endoplasmic reticulum. Sigma-1 receptors have shown promising potential as a therapeutic target for many neurodegenerative diseases, including Alzheimer’s Disease. The location in the endoplasmic reticulum, specifically the mitochondrial-associated membrane, allows the sigma-1 receptors to exhibit a number of neuroprotective properties that could perhaps ameliorate cognitive decline.

Introduction

Alzheimer’s Disease (AD) is the most common neurodegenerative disease, accounting for two-thirds of total dementia cases globally, and is the sixth leading cause of death in the United States; currently, there are approximately 5.8 million AD American patients [1][2]. The statistics highlight that despite the strenuous research put forth to cure Alzheimer’s, its underlying cause for pathology as well as treatment are still areas requiring further scientific investigation [3][4]. AD is identified physiologically by the presence of amyloid beta plaques and neurofibrillary tangles in the brain, and behaviorally by continuous memory and cognitive decline [3][4].

Recent scientific evidence has shed light on sigma-receptors, particularly Sigma-1 receptors, as promising therapeutic targets for neuropathological diseases such as AD [5]. Initially, the sigma receptors were misclassified as a subtype of the opioid receptor in the 1970s but are currently recognized as a distinct class of intracellular proteins [6]. However, the molecular functions that govern these receptors are poorly understood and current research seeks to clarify their ambiguities [3].

General Information on Sigma-1 Receptors

Currently, it is known that sigma-1 receptors are one of the two sigma receptor subtypes, are multi-functional, and have been associated with several neurological disorders, such as amyotrophic...
lateral sclerosis/frontotemporal dementia, AD, and Huntington’s diseases (HD) [7]. These transmembrane proteins are localized in the endoplasmic reticulum (ER), specifically in its microdomains known as mitochondrial-associated membranes (MAM), where the sigma-1 receptors can control inositol trisphosphate (IP) dependent calcium flux from the ER to the mitochondria. In terms of neuroprotective properties, studies have shown that once stimulated, the sigma-1 receptor can cause a neuroprotective effect by stabilizing the IP3R receptor (IP3R), alleviating ER stress, and modulating calcium flux. The IP3R is a membrane glycoprotein complex and serves as a major Ca2+ channel [8] [9]. There are three subtypes of IP3R: IP3R1, IP3R2, and IP3R3, with IP3R1 being examined extensively in terms of brain pathology [13]. Recent studies suggest that dysregulation of IP3Rs may be credited to the pathology of many diseases such as heart disease, exocrine secretion deficit, taste perception deficit, and neuronal degeneration [8] [9][10]. Therefore, the sigma-1 receptors act as intracellular receptors, serving as chaperone proteins that regulate Ca2+ signaling through the IP3 receptor; they are thus accountable for mitochondrial metabolic regulation and enhancing mitochondrial energy depletion and apoptosis [11].

As an integral component in maintaining the structural integrity of the MAM, the sigma-1 receptor serves as a mediary between the ER and mitochondria; recently, evidence indicates that the MAM is crucial in regulating neuronal homeostasis (See figure 1). Consequently, activation of the sigma-1 receptors results in many neuroprotective properties, including the alleviation of ER stress and modulation of calcium influx. Many sigma-1 receptor agonists and ligands also exhibit neuroprotective characteristics, such as overcoming learning and memory impairments from amyloid-β [11]. Furthermore, they promote neurogenesis in the hippocampus [11].

Role of Sigma-1 Receptors in AD

Due to the specific localization of the sigma-1 receptor at the MAM, its regulation of mitochondrial function may be associated with neurodegenerative diseases, such as AD [13]. To start, the ER itself serves a significant role in correct protein synthesis, where incorrect protein folding can result in complications. The pathology of AD, for example, results in the denaturation, or abnormal folding of proteins, specifically the amyloid-β protein. These misfolded proteins then aggregate to form amyloid plaques in the brain.
One of the most common hypotheses for the cause of pathological changes in AD is the calcium homeostasis hypothesis; calcium dysregulation has been highly correlated with the occurrence of ER stress and protein denaturation [3]. Khachaturian first proposed the intracellular calcium hypothesis, postulating that sustained intracellular calcium disruptions are the proximal reasons for neurodegenerative disorders, including AD [3]. This hypothesis has been gaining popularity over the years as many of the other hypotheses, such as the amyloid hypothesis, have failed thus far [14].

Therefore, since calcium dysregulation may contribute to AD pathology, activation of sigma-1 receptors regulating calcium homeostasis, conferring neuroprotection, has garnered attention in the scientific community as sigma-1 receptors being promising therapeutic agents for treating or ameliorating AD [8]. Studies also suggest that sigma receptor ligands may serve essential functions in the metabolism of amyloid-β oligomers in neuron cells, which are extremely neurotoxic and pathogenic agents [15]. Finally, the sigma-1 receptor has been shown to potentially inhibit or even reverse amyloid-β oligomer-induced toxicity and block their signal transduction [15].

References


Neurological Impairment in Duchenne’s Muscular Dystrophy and Its Treatment

Anirudh Kannan

Abstract

Duchenne’s Muscular Dystrophy is one of the most common inheritable genetic disorders within the United States. DMD is caused by a genetic mutation in the gene that codes for the protein dystrophin. Through the past decades, research has been done in an array of both animal (mice) and human models, which are able to roughly reflect the neurological impact of the disease. Additionally, further studies within Dp71, an isoform of dystrophin, have narrowed down the role of the essential protein within the human body. Gene therapy to remedy certain variations of this disease have been commercialized, and a full cure is still being researched.

Introduction

Every day, of the 385,000 children that are born, approximately 110 (0.0286%) will eventually be diagnosed with Duchenne’s Muscular Dystrophy, or DMD, which is one of the most grave forms of heritable muscular dystrophy. Although the 0.0286% incidence rate may seem low, DMD is the most common inherited neuromuscular disorder [1] [2].

DMD is inherited via a frameshift mutation in the dystrophin gene. It is an X-linked recessive trait, so a vast majority of DMD patients are male. This mutation leads to the absence of the protein dystrophin, which is essential in strengthening smooth and cardiac muscle fibers. In addition to muscle weakness, affected individuals face heart problems, such as cardiomyopathy. Dystrophin is also involved in the proper functioning of the Central Nervous System; however, its exact neurological role is still under research. While the function of the protein is unclear, the known neurological symptoms caused by DMD include speech and learning disabilities [3].

Patients with DMD have an average life expectancy of around 27 years and cardiovascular problems become increasingly difficult to deal with by the time patients reach their late 20s. Patients are restricted to a wheelchair for the majority of their lives, as muscle weakness becomes a prominent issue very early in life, during the developmental stages [4].
This article will highlight the neurological issues that are associated with DMD. To provide an understanding of that topic, the animal models of the disorder will first be discussed.

**Animal Models**

The most commonly used model for DMD is the exon-52 deleted (deletion mutation in the 52nd exon of the dystrophin gene) mouse. It was discovered while breeding a colony of lab mice, when one generation of mice were not able to produce dystrophin. Over the years, these mice have been researched heavily, with many brain imaging and neurological capability studies being conducted.

Researchers at the John Walton Muscular Dystrophy Research Center made important discoveries regarding brain mass and histology in the mdx mouse model. Using a combination of MRI and VBM techniques, the researchers were able to estimate the total brain volume (TBV) of the mice. In figure 1, a progression in the increase of TBV in mdx mice can be observed. Surprisingly, the average body weight of the mouse does not follow this same trend and instead decreases. Additionally, it must be noted that the rate of brain volume increase peaks halfway through the trial, further indicating that impairment in DMD is progressive [5].

An experiment involving different trials of the Barnes Maze Test indicated an increase in the time it took for mdx mice to reach the target hole. Over a period of 12 months, the researchers observed that the long-term memory of the mdx mice was greatly deficient compared to the WT. A statistical difference in both the mean latency and the **success score** between the control mice and mdx mice was observed [6].
Understanding the Function of Dystrophin

To fully understand the effect of DMD through the scope of neurophysiology, scientists also study the function of dystrophin on humans. Scientists have focused on a specific isoform of DMD, Dp71, and have been able to understand its function in the body [7].

Researchers were able to gather compelling evidence that suggests Dp71 plays a major role in cell division. By growing and analyzing fresh cultures of Dp71 clones with different amounts of gene expression, researchers noted a statistically significant decrease in the growth rate of the cells as the Dp71 expression decreased [8].

Dp71 is also associated with a certain aquaporin in the CNS [9]. AQP4 is an aquaporin that is highly prevalent in blood-brain interfaces as well as in the extracellular space (ECS) during neuronal activity. AQP4 absent models were found to have increased ECS shrinkage in comparison to a wild type. It has also been found that AQP4 plays a role in clearing out K+ channels during action potentials [10].

One psychological study amongst a cohort of DMD patients around the world identified that FSIQ of DMD patients is significantly lower compared to that of a control sample. The study also found that statistical differences in the FSIQ of patients depends on the location of the mutation on the gene. For example, mutations further along the dystrophin gene sequence affected more dystrophin isoforms, and thus played a detrimental role on the FSIQ of the subject [11].

Current Pharmaceutical Discoveries

Three treatments for DMD have been approved by the Food and Drug Administration (FDA). All three involve some form of exon skipping: a method of gene therapy that involves RNA splicing. Basically, the specified drug allows for a certain portion of RNA that codes for the genetic mutation in DMD to be “skipped” over. This allows for more protein (dystrophin) to be made from the genetic code [12].

This skipping over process is made possible by an “AON,” or an antisense-oligonucleotide (Figure 3). Translation, the process in which proteins are produced from RNA, requires a single-stranded mRNA (messenger-RNA) molecule to
allow for the tRNA (transfer-RNA) to bind to and begin producing the amino acids. When an AON is bound to a specific exon, it is unable to be read during translation, essentially “skipping” over it [13].

Unfortunately, not all cases of DMD can be treated with this therapy. The FDA approved methods of exon skipping only account for roughly ~22% of DMD cases: the drugs Eteplirsen, Golodirsen, Casimersen [15].

Clinical studies are also being performed to bring a certain vector (AAV, Adeno-Associated Virus) into commercial use. In vector mediated gene therapy, a certain gene sequence is packaged into a viral vector. This vector will undergo endocytosis into the target cell and will eventually be transported into the nucleus and integrated into the host genome. If done correctly, AAV mediated gene therapy would allow for the modification of the genome of DMD patients. This modification, if done correctly, could produce the dystrophin protein, making for a long term treatment for DMD [16].

Glossary

- **MRI**: Magnetic Resonance Imaging.
- **VBM**: Voxel Based Morphometry. A computational method of brain imaging that groups different types of neural tissue and compares their concentrations.
- **Barnes Maze Testing**: A test used by researchers to measure spatial learning and memory. The test is conducted in a way where the mouse.
- **Success Score**: calculated by multiplying the number of times a mice pokes its head against a hole with the point value assigned to that specific hole (corresponding to its relative proximity to the target hole).
- **Isoform**: two proteins that are similar in function but do not have identical amino acid sequences; they may originate from the same gene or gene family.
- **Aquaporin**: a type of protein that functions as a water channel between two membranes, performs passive transport due to osmogradients.
- **FSIQ**: Full Scale Intelligence Quotient, a measure that looks at Vocabulary, Patterns, Similarities, etc.
- **Wechsler Intelligence Scale**: An intelligence test that provides a general measure of intellectual ability, involving aspects such as Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed.
- **Antisense-Oligonucleotide**: A small piece of complementary DNA/RNA that can bind to a specific segment of RNA to block its functionality.

References


Scrupulosity: An Overview of “Religious OCD”
Katherine Kaufman

Abstract
Scrupulosity is a mental disorder characterized by obsessive thoughts and anxiety, often with accompanying compulsive behaviors, concerning religion. Recent research developments have pinpointed abnormalities in the orbitofrontal cortex (OFC), anterior cingulate gyrus, and basal ganglia as being related to the presence of OCD, but further research is necessary to explain the relationship between the symptoms and the irregularities. Additionally, broad studies on heredity have shown that scrupulosity is somewhat genetically inherited, but much more research needs to be done before conclusions are drawn. Current treatments for scrupulosity include medication and therapy, but in many cases, individuals with scrupulosity experience symptoms throughout their lives. As more discoveries are made, the treatment of scrupulosity can become more effective, and the negative impacts of the disorder can be mitigated.

Introduction
Scrupulosity, or “religious OCD,” is a subdivision of Obsessive-Compulsive Disorder. Obsessive-Compulsive Disorder (OCD) fits into the larger category of anxiety disorders and is characterized by extreme, repeated thoughts (obsessions) that coincide with repetitive behaviors (compulsions). Scrupulosity involves “pathological guilt or obsession” associated with religion and is accompanied by “compulsive moral or religious observance” [1]. To be considered a disorder, the obsessions and compulsions involved in scrupulosity must be distressing and should inhibit normal function. An estimated 2-3% of people in the US experience OCD at some point during their life, with as many as one third of those people facing scrupulosity specifically. [2,3]

This paper aims to provide an overview of the physical and behavioral characteristics of scrupulosity as well as current diagnosis and treatment practices.

Biological Factors of Scrupulosity
The brain structures involved in scrupulosity are actively being studied. Scientists have identified several structures, including the orbitofrontal cortex, anterior cingulate cortex, and basal
ganglia, that are related to OCD symptoms. Additionally, researchers are making discoveries about the role of neuron circuitry and genetics in scrupulosity, OCD, and anxiety disorders.

A recent study found that patients with OCD have higher levels of activity in their orbitofrontal cortex (OFC) [4]. The OFC is located on the ventral surface of the frontal lobe, just superior to the eye sockets (see Figure 1). It is activated by sensory stimulation, as well as by abstract reinforcers such as winning money. Excess activity in the OFC could explain the intrusive thoughts experienced by OCD patients. However, current research on the OFCs relationship to OCD is not sufficient to establish causality.

The anterior cingulate cortex (ACC), found above and adjacent to the corpus callosum, connects to both the limbic system and prefrontal cortex (see Figure 2). It is involved in complex functions such as decision-making and error-processing. Electrophysiological testing shows a relationship between hyperactivity in the ACC and error-processing abnormalities among OCD patients. ACC activation was positively correlated with the severity of symptoms in patients [5].

The basal ganglia, a group of structures involved in motor control, has also been implicated in OCD. Current research, though incomplete, indicates that abnormalities in the basal ganglia could cause the tics and compulsive behaviors sometimes found in OCD patients [6]. Specifically, researchers have discovered a positive correlation between the volume of the putamen, a key structure in the basal ganglia, and the manifestation of obsessions and compulsions [7]. Additionally, studies show that stimulation of a basal ganglia structure called the subthalamic nucleus “may lessen the severity of obsessive–compulsive symptoms and improve global functioning in patients with refractory, severe OCD” [8].

In addition to the anatomical structures involved in the neuronal level, functions at the neuronal level may play a role in scrupulosity. Hyperactivity in the cortico-striatal–thalamic–cortical pathway, a brain circuit responsible for habits and reward, is associated with OCD [9]. Dysregulation of neurotransmitters in this brain circuit has also been implicated, but how or why these irregularities relate to scrupulosity remains unknown.

It is clear that no single irregularity will be identified as the cause of scrupulosity, but rather multiple circuits and structures with related functions. Because a single cause can’t be singled out, it
is much more difficult to study. Still, researchers have come a long way. Through the findings outlined above, scientists can map out many of the cerebral and cellular structures involved in OCD and scrupulosity. However, this research doesn’t prove whether abnormalities in these brain regions cause OCD or are a result of obsessions and compulsions. Once the relationship between the physical irregularities and the symptoms is better understood, it can be applied to developing diagnostic and treatment techniques.

Another area of study concerning scrupulosity is the genetics’ role in anxiety disorders. Scrupulosity is more common among children whose parents have the disorder, but whether that is due to nature or nurture remains to be proven. Research shows that it is likely a combination of both genetic and environmental factors that causes scrupulosity [10].

**Diagnostic Techniques**

To diagnose scrupulosity, doctors examine the nature of the symptoms. Doctors look for persistent, unwanted thoughts, urges, and/or images that cause marked distress related to morality or religion. These are typically coupled with repetitive behaviors or mental acts that “the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly” [11]. Some examples include praying, reading religious texts, punishing oneself for perceived sins, seeking constant reassurance, or confessing to a religious leader. Other key characteristics of the disorder are that the compulsive behaviors are not logically tied to the obsession and that they are clearly excessive, time-consuming, and distressing.

While diagnosis of scrupulosity may seem straight-forward, that is rarely the case. Because of the nature of the disorder, patients often don’t disclose their symptoms due to “embarrassment, stigma, and the fear of what the obsession might mean or the consequences of revealing it” [12]. As a result, scrupulosity and OCD are often misdiagnosed.

**Current Treatments**

Once a scrupulosity diagnosis has been made, it is typically treated using a combination of medication and therapy. There are three main therapeutic approaches that may be used to address scrupulosity. Cognitive Behavioral Therapy (CBT) is the most well-known type of therapy. Generally, CBT attempts to alter unwanted mood or behavior cycles by challenging negative thoughts. In the case of scrupulosity, CBT might involve learning cognitive strategies to respond to intrusive thoughts without succumbing to anxiety. Exposure and response prevention (ERP), which is sometimes considered a type of CBT, exposes patients to their triggers and teaches them to resist the urge to perform compulsions. A third psychotherapeutic approach to scrupulosity is acceptance and commitment therapy (ACT), where participants learn to use mindfulness to accept feelings or thoughts as natural and move forward with their lives beyond those feelings/thoughts.

Severe OCD and scrupulosity are not solved by therapy alone. Medications are also used to alter levels of neurotransmitters in the brain and reduce symptoms. Types of medications used to
treat OCD include antidepressants (such as SSRIs) and anxiolytics. Certain medications work for some people with OCD, but not others. Currently, psychiatrists largely use trial and error to find proper medications and doses to treat each patient. However, new technologies (i.e. Genesight) may allow doctors to predict what medications will be most effective using genetic testing.

“Tools and techniques including deep brain stimulation, transcranial magnetic stimulation, and electroconvulsive therapy” may be used to treat “patients who fail to respond to standard treatments” [13]. However, these treatments are still in their infancy, and it will be years before such techniques are thoroughly tested and made available to the general population of OCD patients.

Unfortunately, since treatments are not one-size-fits-all, many different tactics may need to be explored before symptoms are effectively addressed. Sometimes, a successful treatment is never found. In fact, “more than a quarter of OCD sufferers receive little or no benefit from these approaches, even when they are optimally delivered” [14]. Complete remission from OCD symptoms is very rare.

An additional barrier to effective treatment is possible religious stipulations. Doctors and therapists must address symptoms without discouraging faithful participation among religious patients. This can be especially difficult when involving faiths where laws and rituals are strictly emphasized, such as orthodox Judaism, or where thought-action fusion (believing that thinking about a sin is the same as carrying out that sin) is taught, such as Christianity. Finally, some religious beliefs may discourage using medication or attending therapy, which can prevent patients from receiving medical treatment.

**Conclusion**

Current understanding of scrupulosity has numerous gaps. In order for effective treatments to be developed, scientists need more information about the roles of neurobiology and societal norms in scrupulosity. Future research is required to determine whether a causal relationship exists between brain abnormalities and manifestations of scrupulosity. Additional research could also shed light on how treatment could respond more effectively to environmental influences or genetic involvement in the disorder.

Even though scrupulosity is a fairly common disorder, scientists know relatively little about it. Scrupulosity is the result of a complex relationship between religious beliefs and obsessive-compulsive symptoms. It can have a devastating impact on those who experience its effects. As a result, it is important that more effective treatments are developed and more research is conducted about this disorder.

**References**


DISEASES AND DISORDERS

Investigating ASD Through a PCT Lens
Arushi Dinker

Abstract
Predictive coding theory (PCT) posits that our brain generates predictions about the world to evaluate incoming sensory information from the environment. Furthermore, PCT serves as a lens from which we can better understand the nature of autism spectrum disorder (ASD). Although modern scientists have studied ASD in a myriad of contexts, they still lack a complete understanding of how it manifests in human brains. Over 75 million people worldwide are affected by autism, and PCT provides a framework to better understand the disorder’s features. PCT can inform us about the nature of neurodevelopmental disorders, like autism, and be used to differentiate various theories on how these disorders might manifest. Clinically, PCT has the potential to be used to establish objective diagnostic tests, which would become valuable for selecting between existing medicinal interventions and for developing behavioral/cognitive therapy programs.

Background

Autism spectrum disorder (ASD) is a developmental disability that drives challenges in socializing, behavior, and communicating [1]. It manifests differently among individuals and is hard to diagnose or characterize because of its broad spectrum of symptoms. Since ASD affects numerous aspects of perception and cognition, one way to break it down is by analyzing ASD through theoretical frameworks of how the brain functions. Predictive coding theory (PCT) can be used to understand many aspects of brain function. It is classically used to describe visual perception but can be applied to any case including processing and interpreting sensory information [2]. PCT’s explanation of how the brain acts on determinations of event probabilities makes it an ideal model to understand how neuronal processing might be affected in cases like ASD. PCT defines predictions as the brain anticipating sensory signals by generating a template against it and then comparing the incoming sensory information to that template [2]. PCT, which is also known as the Bayesian brain hypothesis because it relies on concepts inspired by Bayesian statistics, was popularized by Rao and Ballard in the 90s [3]. PCT is a generalized framework through which we can understand how the brain preempts consequences and decides what actions to take. Multiple factors influence how the brain anticipates sensory signals and forms predictions, other than just individual genetic variance. One source of diversity in brain computations arises from changes in brain development that manifest as neurodevelopmental disorders like autism. In ASD, it’s believed that differences in neuronal wiring of the brain lead to over-connected networks [4]. These differences
relating to the brain’s structure are expressed as behaviors such as fidgeting, obsessions, anxiety, and delayed development. However, through all of this, autism exists on a spectrum and the widespread manifestations can’t be explained by one singular cause and effect scenario.

**Predictive Coding Theory**

PCT operates on the assumption that the brain can form predictions and access them. The brain uses **top-down processing** to match internally generated predictions to external stimulation [5]. Top-down processing is where sensory information is interpreted through neurons and then compared to a template based on preexisting knowledge. This template is then altered if new information contradicts it. In this situation, the incorrect template is termed a **prediction error (PE)** [6]. This act of schema assimilation can be easily imagined with examples from our daily life. Recall, for instance, cell phones. They look very different from previous rotary phones but because they’re more familiar, when asked to think of the word “phone”, most people will imagine smartphones. This is due to prediction errors, over time, overriding our previous encounters with differently shaped phones. Technology evolves so quickly that as years go by, we think first of newer devices and later models are termed PEs. If someone is asked to imagine an Apple laptop, their model has likely been updated to think of the MacBook and not the bulky macintosh from 35 years ago. Predictive signaling reflects a top-down process, where outside knowledge previously acquired through training or learning determines how we react to sensory input. Prediction error signaling shows **bottom-up processing**. Prediction errors occur when sensory information refutes data from the template, or when the information we sense doesn’t match our brain-generated models [7]. This contradicting information travels up to the brain and assimilates into our model.

**Inaccurate Predictions**

Without precise predictions, there is nothing for the brain to compare incoming sensory information to, nor will the brain be able to adapt to new situations quickly. Humans rely on accurate predictions for even the most simple functions. The idea that autism is associated with a decreased ability to make predictions stems from information-processing demands that are intrinsic to the domains typically affected in autism. Sinha et al. argue that the key to making predictions is identifying probabilities of different states in observed events [8]. As we observe incidents, we must be able to determine the likeliness of each component of the incident, to then make a prediction about what will happen next.

**Habituation** is the diminishing of a response to a frequently repeated stimulus. Loosely defined, it means tuning out some recurrent arousal. Through the lens of PCT, the brain habituates to stimulation when familiar stimuli predicted by prior experience result in diminished responses than the response generated by novel stimuli. This experiment measured neural habituation through fMRIs or PET scans and the findings represent if an individual can recognize repeating stimuli. A review of empirical evidence concerning prediction in ASD found that in stimulus constancy (the expectation that a stimulus will be followed by a similar stimulus), the predictability
of a stimulus sequence is directly proportional to the observed neural habituation. If individuals with autism don’t habituate to frequently repeating stimuli, their predictability of stimulus sequences is low. This habituation may be related to the conservation of neural resources and could be important for optimizing one’s response to unanticipated input. 7 of the 8 studies found some type of reduced habituation in the ASD group compared to the neurotypical (NT) group. This included decreased neural habituation to repeated tones. These results suggest a widespread reduction in neural habituation to repetition. Tam et al. also found that the ASD group exhibited less habituation of reaction time over repetitions of working memory involving faces, while Vivanti et al. found decreased habituation of gaze fixation frequency to repeating shapes [9].

These results demonstrate deficiencies in habituation to and recognition of pattern sequences in individuals with ASD. The inability to recognize these pattern sequences can explain deficiencies in diagnosing criteria such as language processing, social interactions, and behavior. Without the shortcuts, NT individuals use to recognize patterns and then act on their predictions, language processing, and social interaction are tasks that become infinitely harder to perform well.

There are two main categories under which hypotheses of inaccurate predictions in individuals with ASD fall: predictive process impairment and predictive learning impairment.

**Predictive Learning Impairment**

Sinha et al. argue that ASD is characterized by inaccuracies in learning the probabilities that govern changes in events over time, which are necessary to make accurate predictions with an appropriate degree of certainty. This assertion is explained in the equation: $P(B|A, Δt)$, where $P(B|A)$ is the probability of events A and B, and the value is graphed over time. The current domains believed to serve as diagnosing criteria for autism: language processing, social interactions, and behavioral repertoire, are modeled as temporally evolving Markov systems [8]. This means that executing these diagnosing criteria depends on an individual’s ability to gauge the probability of future states depending on their interpretation of the current state. For example, if two individuals are arguing about where to eat, they need to determine how likely an agreement is to gauge the probabilities of the states of eating at different restaurants. If one fails to evaluate the probability of an agreement, they can’t predict if or where they’ll eat.

An impairment in detecting and learning predictive associations may be because of stimulus overselectivity, referring to individuals with autism having a tendency to learn to associate only one perceptual aspect of a complex cue with an outcome. An impairment in detecting subtler contingencies could explain the consistent predictive impairments in studies where predictions were dependent on social priors. If individuals cannot connect multiple parts of social interaction to an event, they are unlikely to form an accurate prediction for those multiple parts.

**Predictive Process Impairment**
The idea that individuals with ASD have impairments in updating their predictive models stems from the **hypo-prior hypothesis** introduced by Pellicano and Burr. Pellicano and Burr hypothesized that the brain of ASD-affected individuals draws less heavily on priors, creating a perceptual experience more loyal to the current sensory information [10]. This account locates the key predictive difference in ASD as a difference in the modification of internal prediction models. Studies showing the reduced influence of perceptual priors provide weighty evidence of impairment along the lines proposed by Pellicano and Burr. Van de Cruys et al. indicate that ASD is not characterized by an impairment in employing predictions but instead by differences in the process of learning or schema accommodation [11]. There are also consistent differences between ASD and NT groups in spontaneous noticing that a predictive value has changed. Individuals with autism perform worse on open-ended tasks because, without explicit instruction, they have to rely on their prediction processes. The deliberate predictive movement seems to be unaffected by ASD, explaining why individuals with autism are high-functioning outside of social or other complex behavioral situations.

Such impairment could be related to learning differences in the predictive behavior, rather than in learning the underlying predictive associations. In other words, learning to move in anticipation may require learning to expect yourself to move in a certain way in a certain situation. Predictive processing is not just about predicting the external environment, but also about predicting your function within that environment and the cause-effect relationship between the two.

**Sensory Overload**

Predictive coding relies on the ability to interpret sensory information and compare predictions to the current stimuli. Comparing predictions with incoming sensory stimuli requires intensive computation from the brain. Sensory overload occurs when the brain is overwhelmed from the disruption of the balance between internal priors and incoming sensory information, with too much of the latter. Increased sensory overload explains the **magical world hypothesis** which theorizes that if individuals with autism experience sensory overload, this new sensory input may override their internal predictive models. This override causes individuals with autism to continually update their model of the world whenever they encounter new information. As they shift their prediction models of phenomena, it seems like their world is magically changing. Sensory overstimulation is a well-documented feature of autism and is often used in diagnosing the disorder [12]. When the brain’s predictions are constantly updated because of incoming sensory information, sensory overload occurs. In NT individuals, some sensory information is filtered out or deemed fallacious, meaning that the previous predictions stay intact. It’s hypothesized that PCT can manifest as sensory overload because individuals with autism cannot filter incoming sensory information and instead use it to constantly update their models [13]. Impairments in an individual’s predictive process could cause sensory overload when individuals are more loyal to the current sensory information rather than their priors.
In the brain, incoming sensory information can take 3 general routes: 1) update internal models with new sensory information, 2) determine that the sensory information is a chance deviation and not update the model, 3) act to make this sensory input deviation a reality. If so far, the sensory information that determined the model has high precision, the brain pays special attention to this variance. If there’s low precision, the brain is more likely to determine this variance as chance [14]. The preciseness of the conflicting sensory information determines if the individual’s model is updated.

If individuals with autism give low credence to their predictions, “bigger-idea” patterns are sacrificed and sensory overload occurs. This connects to the magical world hypothesis because if an autistic brain updates its predictions almost every time it encounters new sensory information, the world will keep changing for individuals with autism. People with autism may have trouble recognizing patterns or continuity because their ideas of the world change so often. Therefore, a world that seems predictable to neurotypical people can strike people with autism as volatile. This idea is supported by data that shows individuals with autism as unlikely to habituate to sensory inputs and recognize them as patterns. Instead, they’re likely to fixate and pay extreme attention to detail. As evidenced by experiments like deWeerdt’s study of habituation to recurring beeps, where neurotypical people’s spike in brain activity declined as repeated beeps were played over and over again, it’s characteristic of NT to habituate to repeating signals [13]. However, in people with autism, the spikes stayed the same over the course of the experiment, if not intensified at a point. This demonstrates a fundamental distinction between habituation or prediction processes between autistic and NT individuals, a difference that can be explained using the PCT framework.
Individuals with autism also have problems deciding what their brain should listen to because of the low credence of their predictive models. They have low credence but high precision in their internal predictive models, making them favor any discrepancy in sensory information. When your brain is overwhelmed by incoming information, your body can enter a flight-or-fight mode (sympathetic nervous system activated). This results in an unsafe or panicky feeling, and long-term activation of the sympathetic nervous system can result in overexposure to cortisol and other stress hormones that can disrupt almost all the body’s processes. Individuals with autism don’t just have to deal with sensory overload, but they also have to update their predictive models every time they encounter more information as shown in Figure 1, increasing the degree of stress they would feel in new situations. These extensions of the sensory overload hypothesis explain symptoms identified in ASD like repetitive body movements, social communication challenges, gastrointestinal issues, unusual emotional reactions, anxiety, stress, etc.

**Research Evaluation**

PCT is a theory of how the brain functions, meaning that much more research is required to understand if neural circuits do engage in Bayesian computations to the degree that PCT theorizes. Nevertheless, PCT is the key to understanding the causes behind neurodevelopmental disorders like schizophrenia and autism which deal with impaired functioning because of faulty predictions; more experiments focused on this theory are crucial [16]. Although there is a good amount of literature on PCT, the exact neural circuits behind a biological manifestation of this theory are still unidentified, nor have we found genes that influence them.

**Discussion**

Through variances in the PCT framework between NT and individuals with autism, we can clue into how autism manifests in humans. PCT can either be varied through learning impairments, process impairments, or information valuation impairments. If individuals are unable to detect and learn predictive associations, their predictions will be inaccurate and it will inhibit them from performing well in interpretive situations. Similarly, if individuals can form predictions but are unable to employ them, it will also cause an inability to socialize. An inability to assign the appropriate importance to information means that individuals with autism could use erroneous information to update their predictions. Their predictions will end up less accurate because of the lack of solid data and their world will seem constantly changing and evolving because their impression of it will be constantly updated. Impairment with predictive learning would explain why individuals with autism do not perform as well as NT with experiments concerning social priors. Both predictive process impairment and information filtering impairment account for sensory overload, a commonly noted characteristic of individuals diagnosed with autism. Predictive process impairment also more concretely demonstrates why individuals with autism are high functioning outside of social/complex situations. These 3 routes of visualizing autism all present possibilities to establish criteria for diagnosing autism as well as evaluating the best courses of care. More studies of these potential interpretations would greatly benefit the 75 million people globally affected by autism [17]. PCT could also extend to elucidate other neurodevelopmental disorders like schizophrenia.
because they manifest impaired functioning based on faulty predictions [16]. Based on the 3 routes proposed, treatments like therapy or medicinal interventions could be refined to choose the most effective method of care. Specific information processing and filtering tests for autism would be useful to distinguish between the 3 routes proposed in this paper.

Glossary

- **Predictive Coding Theory (PCT):** brain uses internally generated models to understand the world around us, evaluates outside information by top-down processing and updates model by bottom-up processing.
- **Top-down Processing:** sensory information is interpreted through neurons and compared to the brain's template based on preexisting knowledge.
- **Bottom-up Processing:** senses detect information which is put together in the brain without prior knowledge.
- **Prediction Error (PE):** information that contradicts the brain's model.
- **Neuropredictive (NT):** individuals with typical neurological development or functioning.
- **Habituation:** diminishing of a response to a frequently repeated stimulus.
- **Markov Systems:** system that can model distinct but interconnected states that can be progressed through according to fixed probabilities.
- **Stimulus Overselectivity:** tendency of individuals with autism having to learn to associate only one perceptual aspect of a complex cue with an outcome.
- **Hypo-prior Hypothesis:** brain of ASD-affected individuals relies less on priors and is more loyal to current sensory information.
- **Magical World Hypothesis:** due to increased loyalty to current sensory information, brains of ASD-affected individuals constantly update their models, creating an ever-changing “magical” world.

References


[12] Dinker, Arushi. (16/10/2021). Figure 1.


The Ethical Roadblocks of Consciousness in Human Brain Organoid Research and a Word of Warning

Yue Yu

Abstract

Human brain organoids (HBOs) are three-dimensional in vitro structures developed from human induced pluripotent stem cells (iPSCs) that imitate the development of the human brain. In recent years, HBOs have shown great promise in research in multiple fields, from developing medical treatments to investigating consciousness. Though simple as of now, there are growing concerns that HBOs could acquire sentience and even consciousness in the future, becoming capable of experiencing pain and suffering from their usage. It is thus imperative to decide upon suitable moral statuses for HBOs and create ethical regulations that outline what is permissible and impermissible to HBO research before that point in time arrives. The first issue to tackle is determining consciousness in HBOs, which is currently approached by drawing inferences from the Perturbational Complexity Index and structural features of HBOs. The second issue is in examining the possibility of valenced conscious experiences in HBOs. HBO transplants also present unique issues, namely the treatment of chimeras with increased vulnerability to suffering, and the uncertain outcomes to conscious viewpoints when two conscious HBOs are merged. As of now, proposals to ethical regulations advocate for weighing potential costs with benefits and overall minimal usage of HBOs in research. Such proposals cannot be improved without further understanding of HBOs, which is impossible before research is allowed on ethical grounds. Due to this, “sacred” usage of HBOs in early stage research could one day emerge, for which further precautions need to be taken.

Introduction

Back in 2008, a group of Japanese researchers pioneered the research of human brain organoids (HBOs) by extracting the self-organized formation of functional cortical tissues from embryonic stem cells in mice [1]. Since then, HBOs have shown remarkable potential and have been
used in the research of diseases such as schizophrenia, autism spectrum disorder, Zika virus-induced microcephaly, HIV-acquired neurological diseases, and in the research of neurological effects of the SARS-CoV-2 virus [2][3][4][5][6]. Furthermore, it demonstrates promise in research of consciousness, though not without ethical concern [7]. Nonetheless, efforts have been made to evaluate consciousness in HBOs, investigating their moral relevance and proposing frameworks and principles for their ethical usage. This paper will discuss these efforts and warn against the resulting possibility of “sacrificial” HBO usage in early stages of consciousness research.

Current Obstacles

Currently, two significant problems concerning research of consciousness in HBOs exist: evaluation of phenomenal consciousness and investigation of the moral relevance if consciousness is identified. The first refers to determining the presence of consciousness from an HBO, along with investigating its capacities of having sensations, experiences, and degree of sophistication. The second addresses the moral implications that this consciousness brings [8]. Some assume that an entity’s moral status is determined by the complexity of its consciousness, which can be easily refuted when observing the current treatment of animals in biomedical research. This assumption further implies that HBO’s deserve even less protection from harm than animals in analysis, a flawed conclusion when considering the distinct form as well as lack of form (e.g., lack of body and sensory systems) that HBOs have, which contribute toward experiences, interests, and suffering that are perhaps unknown to any natural conscious entities. Therefore, before jumping to conclusions, it is necessary first to be able to evaluate consciousness in HBOs.

Approach by PCI

Various approaches have been proposed for detecting and evaluating consciousness in HBOs. Many highly anticipated strategies are non-introspective methods based on the Perturbational Complexity Index (PCI), presented in 2018 [9]. The PCI is a metric gauging the complexity of an integrated response of the thalamocortical system to a direct perturbation, often delivered by transcranial magnetic stimulation (TMS). TMS is a non-invasive form of brain stimulation where a changing magnetic field is used to change the currents in specific areas of the brain by electromagnetic induction. Thalamocortical systems with more sophisticated consciousnesses are believed to generate more complex responses after stimulations by TMS, thus observing complex responses can be used to infer the existence of more advanced consciousness [10]. It has already proven effective in detecting consciousness in unresponsive patients [11]. Though this approach offers little information about the experiences an HBO may have, it may prove helpful in screenings for consciousness and comparing the degree of development between organoids.

Approach by structure

Another approach to evaluating consciousness is observing an HBO’s structure [12]. It is demonstrated that some cortical organoids already display network activities resembling oscillatory patterns observed in the developing brain [13]. This suggests possible links may exist between HBOs and the developing brain. It has also been shown in humans that “the capacity for conscious perception of pain can arise only after thalamocortical pathways begin to function, which may occur in the third trimester around 29 to 30 weeks gestational age” [14]. Thus, by comparing the structure of an HBO to such structures of fetuses at 29-30 weeks gestation age, we could approximate the capacities of perception and consciousness an HBO may have. However, it is more commonly
suggested to err on the side of overestimation. So it would be safer to assume that “a brain organoid lacks even a rudimentary form of consciousness until it resembles the brain of a fetus at 20 weeks' development” and “beyond this point, we should treat brain organoids as if they could plausibly possess some degree of consciousness” [12].

One implication of this approach is that it confirms current HBOs as unlikely to have such perceptions and consciousness, as can be observed in Figure 1, by the comparable disorientation and disorganization of cells in the HBO compared to a developing human brain. Unfortunately, this approach could be limited to the early stages of HBO development since HBOs often become more differentiated as they are developed to suit the needs of specific research, for example, the development of optic nerve-like structures in some [15]. Nonetheless, it provides another useful reference point.

**Implications of valency**

In relation to the second problem of the moral relevance of consciousness, valency becomes an important consideration to keep in mind. It has been argued that the morally significant conscious experiences must be valenced experiences, or experiences that are intrinsically good or bad to the experiencer, giving them experiential interests, as non-valenced occasions arguably do not bring suffering, or at least, to a lesser degree [17]. This argument reduces the ethical barriers to research that uses organoids that only generate non-valenced experiences. These are also likely to be the organoids more commonly used in early-stage HBO research. It, therefore, makes much of the previously impermissible research permissible. However, determining the valency of experiences is another challenge, as it is extensively rooted in subjectivity.

**Issues of transplants**

There are also unique issues related to HBO transplants. First, it is important to understand that HBO transplants are categorized into two divisions, symmetric and asymmetric. Under the category of symmetric transplants, there are further divisions of phenomenal unity and compartment. Symmetric transplants refer to when “two autonomous, continuous minds will be connected,” while in asymmetric transplants, only brain organoids that “realize partial psychological states” will be transplanted [8].
In vivo transplants are currently mostly asymmetric transplants. Therefore, the statuses of chimeras need to be established. It has already been found that transplant of human glial progenitor cells to mice enhances long term potentiation (LTP) in the adult murine hippocampus, as well as learning, shown through various behavioral analyses, such as Barnes maze navigation, object-location memory, and contextual and auditory fear conditioning [18]. Learning and memory are undoubtedly very closely related to consciousness. It gives rise to noetic consciousness and allows organisms to “cognitively operate on, objects and events, and relations among objects and events, in the absence of these objects and events” [19]. It’s likely that as chimeras develop higher levels of cognitive abilities, as their consciousness develops. Therefore, when transplanting HBOs in vivo, there is a risk that we make these host animals more vulnerable to suffering, and previously non-valenced experiences now become valenced. It then becomes necessary to re-evaluate the consciousness of this newly created chimera.

Symmetric transplants mainly bring issues related to viewpoints of consciousness. When two minds are biologically fused, they may either coexist, or one may disappear entirely. The former results in similar ethical issues found with conjoined twins, while the latter “casts doubts on the moral permissibility of transplantation”[8]. These issues may be especially pressing since HBOs transplants have much potential for medical treatments. Nonetheless, these problems are not likely to be overcome before the previous issues are dealt with.

Proposed frameworks

As of now, several principles and ethical frameworks for research have also been proposed. Some have suggested only allowing HBOs when the benefits justify the harm and suffering inflicted. In contrast, usage, degree of harm, period of harm, and cognitive capacities of the HBOs used should be minimalized [15]. Further modifications have been proposed since, now considering the valency of experiences and the possibility that consciousness may be present in all HBOs [20]. Although perhaps still too ambiguous for usage, this nonetheless moves the discussion forward, shifting the focus towards fairly and accurately weighing the benefits of HBO usage against harm, investigating the harm that may be inflicted, and screening cognitive abilities to reduce exploitations.

Words of warning

Unfortunately, the process of exploring these aspects is unlikely to be without errors and mistakes, even with ethics in mind, in part due to the flaws in the methods discussed above, as well as the subjectivity related to this research. Without promising alternatives, proposals to use HBOs in the early stages of examination, before regulations are complete could emerge, arguing that proposed research would generate much-needed knowledge of HBOs, leading to better regulations and reduced harm to HBOs in the long run. In such cases, one should keep in mind that the yield of effective results cannot be guaranteed, and therefore harm to HBOs is not always justified. Meanwhile, loopholes and possible exploitations must be vigilantly checked for. If this is acceptable, then perhaps with continuous adjustments to methods and regulations, there will be a better chance of dealing with these ethical issues.
Conclusion

We have thus discussed the current major roadblocks and progresses in the field of ethics of HBO research related to consciousness, as well as the possibility of “sacrificial” usage of HBOs in the early stages of HBO development to facilitate understanding and better protect HBOs in the long run. Though current HBOs are still far from developing noticeable consciousness and facing these ethical problems, it is imminent, especially since the recent achievement of vascularization in HBOs. Continuous collaboration between researchers of different fields is crucial, as well as involvement with the public and governments around the world, to prevent public unrest and judicial loopholes in other countries. Such efforts will be necessary, as behind HBO research lies the greater moral imperative to protect them while advancing neuroscience, medicine, and socie

References


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