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FEATURED ARTICLES

‘Looking into Criminal Minds: ‘The Neurological Basis of Crime’
- Aarsha Shah

‘The Role of the Amyloid Precursor Protein Gene and Copper in Alzheimer’s Disease’
- Emily Barron

‘Trust Your Gut: How the Gut Microbiome Affects Brain Function’
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Letter From the Editors
Sojas Wagle, Aayush Setty, Kareena Thakur, Ashvin Kumar, Kunal Dhirani, Anca-Mihaela Vasilica, Kyle Sugita, Shyam Soundararajan, and Annie Pan

Dear Readers,

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

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

Aayushi Gandhi talks about how the gut microbiome affects the brain function, Quan Le and Urvi Sharma explores psychopathy and sociopathy, Rucha Kamat gives an overview of stress, Srikar Chintala covers out-of-body experiences, and Aarsha Shah sheds some light on the neurological basis of crime.

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

Best Regards,
Sojas Wagle - IYNA Journal Editor-In-Chief
Aayush Setty - Managing Editor
Kareena Thakur - Senior Editor
Ashvin Kumar - Senior Editor
Kunal Dhirani - Senior Editor
Anca-Mihaela Vasilica - Senior Editor
Shyam Soundararajan - Senior Editor
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An Exploration of Psychopathy and Sociopathy

Quan Le and Urvi Sharma

Introduction

Modern society often portrays psychopathy and sociopathy as conditions characteristic of serial killers and terrorists, such as Charles Manson. However, only one percent of the general population is considered psychopaths and sociopaths [4]. People with psychopathy and sociopathy acquire the disorder from a combination of genetic predispositions and environmental factors [6]. This article will address the various aspects of psychopathy and sociopathy. First, common misconceptions about both disorders will be identified. Following this explanation, an overview of symptoms, treatments, and methods of diagnosis will be provided. Finally, the anomalies in brain structure relative to normal human brains will be discussed.

Misconceptions

There are quite a few misconceptions regarding both psychopathy and sociopathy, and in some cases, these terms are used interchangeably. The facade of a sociopath is defined as having no feelings and a cold and heartless personality [5]. Author Ray Bohn states, “A lack of emotion has always seemed advantageous [4].” Bohn is stating that the absence of emotion correlates with the idea of having one’s decisions be solely influenced by logic. Another notion associated with sociopaths is their poor impulse control, a symptom commonly associated with Attention Deficit Hyperactivity Disorder (ADHD) and Attention Deficit Disorder (ADD).

A psychopath is defined as a person with an extreme inability to empathize with other beings [1]. A sociopath also lacks the ability to show an extroverted demeanor, but this behavior is equally influenced by genetics as it is by the surrounding environment [1]. However, many have misinterpreted this definition, leading to a commonly held notion of psychopaths being uncommunicative. Furthermore, this foments the belief that most psychopaths are introverted, but in actuality, some possess qualities that are a mix of both introversion and extraversion [9].

Diagnosis and Symptoms
Even though psychopathy is commonly misused to describe those with mental illnesses, psychopathy is not an officially recognized disease. The American Psychiatric Association equates psychopathy with antisocial personality disorder (ASPD) and describes psychopaths as individuals who show patterns of manipulation and violation to others. Psychopaths tend to lack remorse for their actions, display high levels of self-confidence, and exploit others for their own benefit. Other common signs of psychopathy include socially irresponsible behavior, inability to distinguish between right and wrong, tendency to lie often, and possible recurring problems with the law. Researchers estimate that 1 percent of the overall population is considered psychopathic and psychopaths comprise around 4 percent of corporate CEOs [4]. From these statistics, it can be assumed that there is a broad range of people afflicted with psychopathic tendencies; however, many of them are not fully diagnosed with ASPD. ASPD can be difficult to treat because people with the disorder will often deny behavioral anomalies, depriving themselves of proper psychological treatment [4]. The diagnosis for ASPD generally begins at age 15 [4]. A mental health professional initiates this process by conducting a full mental health evaluation. The professional evaluates the person’s thoughts, feelings, behavioral patterns, and relationships. Their symptoms are compared to ASPD symptoms along with conduct disorder (CD), with which children rebel against authority figures, and oppositional defiant disorder (ODD), with which children attempt to control others through intimidation and aggression. However, a true ASPD diagnosis is not made until the age of 18 [4].

A sociopath is a person defined by not only a lack of empathy, but also a surplus of deceit and selfishness. Sociopaths tend to use tactics like personality shifts in order to empathize and please others for their own benefit. A person who possesses this disorder is often brought up in an abusive or neglectful household and is at a higher risk of exhibiting the aforementioned traits [5]. Genetics often play a role in developing these sociopathic behaviors [5]. People with an antisocial or alcoholic parent are at an increased risk for this disability [5]. Research shows that as much as 50 percent of a psychopathic diagnosis is caused by genetics, while the remaining 50 percent is determined by environmental factors [5]. Sociopathy is particularly detrimental to children and teenagers, as it can lead to personality disorders in adulthood. While it is unusual for a sociopath to seek professional help, interventions and therapy can manage symptoms as well as side effects. Side effects of sociopathy include aggression, hostility, and impulsivity [8]. Children who exhibit severe symptoms of sociopathy and do not complete therapy often have a bleak prognosis and are more likely to be diagnosed as a sociopath at the age of 18. Currently, no medicinal treatment has been developed for people to combat this disorder.

Differences in Brain Structure

Sociopaths and psychopaths seem similar to the average person from the outside, but a deeper look into these syndromes reveal that they are quite different. They can both take a significant toll on one’s physical health as well as the health of those around them. People with psychopathy tend to have a lower amount of connections in their ventromedial prefrontal cortex, the part of the brain accountable for actions such as empathy and guilt [2]. Sociopaths also have a lower amount of connections than the norm. Their amygdalae, which are responsible for
“mediating fear and anxiety,” also exhibit differences from normal amygdalae by being smaller by 18 percent [7].

Michael Koenigs, an assistant professor of psychiatry at the University of Wisconsin School of Medicine and Public Health, states, “This is the first study to show both structural and functional differences in the brains of people diagnosed with psychopathy. Those two structures in the brain, which are believed to regulate emotion and social behavior, seem to not be communicating as they should.” Such anomalies demonstrate how the brains of people with such disorders may differ from normal human brains, leading to the plethora of aforementioned symptoms.

There is no question that psychopathy and sociopathy are real conditions that interfere with the capacity to empathize. Societal misconceptions can result in misinformation and negative, unwarranted judgment. People with these disorders should be treated with the same respect as everyone else.

References


Synesthesia: Hearing Colors or Tasting Shapes?
Deekshita Sundararaman

Abstract
Synesthesia is a remarkable instance in which one property of a stimulus evokes a second experience not usually associated with the first. There are many variants of synesthesia, including synesthetic experiences of color, taste, touch, and sound. In the last few decades, research has highlighted the classification and mechanisms underlying this unique phenomenon. The following article explores the types of mechanisms that contribute to synesthetic experiences, as well as the broader cognitive and perceptual traits associated with synesthesia. Furthermore, it discusses the different types of synesthesia and their applications.

Background
Synesthesia was first discovered by Georg Tobias Ludwig Sachs, a German physician who reported colored vowels as part of his Ph.D. dissertation. Since then, the father of psychophysics, Gustav Fechner, brought attention to this phenomenon through his empirical survey of colored letter photisms. Today, synesthesia is commonly known as an anomalous blending of the senses in which the stimulation of one modality simultaneously produces sensation in a different modality. Synesthetes can hear colors, feel sounds, and taste shapes. This peculiar phenomenon is as rare as it is strange: the estimated occurrence of synesthesia is rarer than one in every 20,000 people [18]. More than being able to correlate seemingly unrelated things, many synesthetes report having an unusually good memory for things such as phone numbers, security codes, and polysyllabic anatomical terminology because digits, letters, and syllables take on such a unique panoply of colors.

Classification
Several researchers have distinguished synesthesia from other psychological phenomena using visual imagery and certain forms of imagistic memory. The primary characteristics used to diagnose synesthesia are automaticity, reliability, and consistency [2]. Firstly, synesthetic associations are automatic in nature – they are produced outside the intentional control of the individual and cannot be directly inhibited [3]. The automaticity of synesthesia helps to distinguish
it from paradigm cases of mental imagery. While hearing a certain sound may lead one to imagine certain scenes or colors; for example, such visual imagery is typically under a significant degree of intentional control. An individual can typically start or stop imagining something at will. However, while synesthetetic responses possess qualities similar to those exhibited by mental imagery, they are automatic and cannot be controlled thus distinguishing them from other psychological phenomena.

Secondly, synesthetes are typically able to reliably experience synesthetic responses when presented with triggering stimuli, meaning that whenever synesthetes come into perceptual contact with the triggering stimulus, their responses will be induced [4]. These responses are not transient or inconsistent, though they can be when they are induced neuropharmacologically through the use of psychoactive, hallucinogenic substances [4]. Furthermore, synesthetes often experience this phenomenon from early childhood, which helps distinguish the condition from ordinary associations grounded in memory. Many synesthetes often associate vivid mnemonic imagery with specific smells or sounds; for example, and these memories arise automatically.

Finally, although there may be slight variations among synesthetes, the majority of the synesthetic associations within an individual appear to be relatively consistent over time [19]. For example, specific auditory tones may tend to elicit the same types of color-specific responses. To test this consistency, neuroscientists typically administer a series of tests over a period of time. The rationale is that if an individual has synesthesia, their consistency of responses in the retesting phase will be much higher compared to those without synesthesia [5]. This was seen in Baron and Cohen’s study, which reported that 92.3% of reported synesthetes gave consistent responses when they were retested a year later without warning [19].

**Types of Synesthesia**

Out of all variants of synesthesia, grapheme-color synesthesia is the most prevalent. Grapheme-color synesthetes tend to associate written letters and numerals with colors. For example, this type of synesthete may always associate the number seven with the color red. While there are some similarities among the associations made by all grapheme-color synesthetes, it is highly unlikely that two people with this form of synesthesia will experience the same associations. In this form of synesthesia, cross-wiring occurs between the brain’s color and number area, which are both located in the fusiform gyrus [6]. The neural substrate of synesthesia has been thoroughly studied in grapheme-color synesthesia using both psychophysical tests and functional imaging: several groups have demonstrated that simple achromatic graphemes activate both grapheme regions, as well as color area V4, a region of the visual cortex that shows a stronger response to colors than to grayscale stimuli, in the brains of synesthetes, which is consistent with the view that synesthetic colors are sensory in nature [14]. Predicting this finding of “cross-activation” between grapheme and color regions, researchers Ramachandran and Hubbard proposed that synesthesia results from an excess of neural connections between associated modalities, possibly due to decreased neural pruning between adjacent regions that are interconnected in the fetus [15]. Consistent with this suggestion, a number of studies have demonstrated anatomical differences in the inferior temporal lobe near regions related to grapheme and color processing in synesthetes,
including increased fractional anisotropy and gray matter volume. This can sometimes make grapheme-color synesthesia an aid to the synesthete’s memory and learning.

The second variant of synesthesia is ordinal linguistic personification, a form of synesthesia in which ordered sequences, such as ordinal numbers, days, months and letters are associated with personalities or genders. These synesthetes tend to perceive ordered sequences such as numbers, letters, days, and months with inherently distinct personality traits or gender. As with many other types of synesthesia, the associations are roughly constant for the synesthete but are not necessarily the same among synesthetes who exhibit the condition [7]. While ordinal linguistic personification has been noted to co-occur with other forms of synesthesia, it has been shown to co-occur with greater frequency in synesthetes who display grapheme-color synesthesia [7]. An example of this type of synesthesia is when an individual perceives the letter “A” as female and the letter “T” as male, or the numeral “5” as sneaky.

The third variant of synesthesia is chromesthesia, also known as sound-to-color synesthesia. In chromesthesia, sounds heard by the synesthete are associated or perceived as particular colors. While the synesthete hears the sound just like everyone else, they simultaneously and naturally experience a color that remains more or less constant with that specific sound. Similar to the pairs found in other types of synesthesia, the pairings in chromesthesia are consistent for each synesthete but are not automatically the same for another synesthete with chromesthesia. What researchers have discovered, however, is that synesthetes tend to associate high pitched sounds with light, bright colors [6]. Low pitched sounds, on the other hand, are more likely to be matched to darker colors. There is also some evidence to suggest this phenomenon can be found (to a lesser extent) among non-synesthetes. Subgroups among chromesthesia synesthetes include those for whom the condition is triggered by all types of sounds and those for whom musical notes only generate their sound-to-color associations. Furthermore, some of these synesthetes report that the colors are only evoked by people’s voices. A note-worthy group related to chromesthesia synesthetes are people who have color-to-sound synesthesia when colors are perceived as sounds. In instances where an individual is identified as having both sound-to-color and color to sound synesthesia, the pairings often remain the same in both directions.

Another variant of this phenomenon is seen in spatial sequence synesthesia, or visuo-spatial synesthesia, a common condition in which ordinal sequences such as months, numbers or the letters of the alphabet are perceived to occupy spatial locations in the mind’s eye or peripersonal or
extrapersonal space [8]. Basically, a synesthete who experiences this phenomenon may see the spatial arrangement with their “mind’s eye” or in the actual space around them. For example, these synesthetes may think of the letter “A” as farther away in space than the letters “B” or “C.” They might also perceive the time on a clock as located in the specific points in the space around them. Furthermore, these individuals have been shown to have a superior ability to recall events, as well as the ability to see into the past or travel through time [9]. There have also been studies that indicate a heightened ability among persons with spatial sequence synesthesia to recall the events which have occurred in their own lives. This condition, known as hyperthymesia, is often linked to autism and savant syndrome [9].

The fifth variant of synesthesia is mirror-touch synesthesia, a rare condition that causes individuals to experience a similar sensation in the same part or opposite part of the body that another person feels. The mirror-touch sensation can be activated by both real-life and in-person situations, as well as by watching someone on a screen. While most other forms of synesthesia are developmental, mirror-touch synesthesia can also be acquired after sensory loss following an amputation [10]. This was seen in Dr. Ramachandran’s mirror box experiment, where amputees reported that the pain in their “phantom” limb was eased when they simply viewed their arm moving in the mirror box. A few other examples include a mother sensing a stethoscope on her back when the doctor places a stethoscope on her child’s back or feeling the pain of an athlete simply by watching them get injured on television. Understandably, some studies of mirror-touch synesthesia have linked it to synesthetes having a heightened sense of empathy for the pain being suffered by others [10]. The condition has proven to be helpful to synesthetes working in certain professions, such as doctors and massage therapists.

The rarest out of all the variants is auditory-tactile synesthesia, also known as hearing-touch synesthesia. In this instance, sounds heard by the synesthete produces a tactile sensation on certain areas inside and outside of the body, which is caused by the cross-wiring of the auditory and somatosensory cortices in the brain [11]. There are a plethora of sensations that can be experienced, which tend to vary among synesthetes [11]. For example, a sound that feels like a tingling sensation to one synesthete may be perceived by another as the pressure we normally associate with something pressing against our skin. Since the primary stimulus that produces a particular sensation varies among auditory-tactile synesthetes, the same trigger may produce a variety of responses among different individuals. There are occasions when synesthetes describe the perceived tactile sensation as pleasant but on other occasions, sounds can produce sensations that are distracting, uncomfortable or outright painful.

Figure 2. Dr. Ramachandran’s famous mirror box is used to cure pain or uneasiness in the phantom limbs of amputated patients [17].
Another rare form of synesthesia is number form synesthesia, where the synesthete involuntarily sees a mental map of any group of numbers they think about. This phenomenon is caused when the synesthete’s brain takes place between close-lying regions within the parietal lobe which governs spatial and numerical cognition [12]. The arrangements in number form synesthesia differ from the conventional number line we are all taught in school and could be idiosyncratic and unchanged throughout the synesthete’s lifetime [12]. The synesthete may have a particular form for months of the year and another for dates. Furthermore, the number of forms that are perceived are not related to colors and do not necessarily possess any form of symmetry. The number of forms may be complex or simple and may involve curved or straight lines or a combination of both. Because of this, number form synesthetes process information more efficiently when it is presented in a manner that matches their brain’s number form and may have difficulty learning conventional mathematics [11].

The eighth variant is lexical-gustatory synesthesia, a rare form of synesthesia in which spoken and written language causes individuals to experience an automatic and highly consistent taste/smell. Like other forms of synesthesia, lexical-gustatory synesthesia is also known to develop during early childhood [20]. Synesthetes with lexical-gustatory synesthesia tend to make linkages between word and foods they were exposed to as children. The experience of the evoked sensations is often linked to the sound of the word, but some researchers think it may be connected to the meaning of the word, as well [20]. However, not all words and sounds induce the same intensity or complexity of taste in the synesthete. There are certain words and sounds which produce no taste response at all.

Finally, the last and newest form of synesthesia is misophonia, a phenomenon in which certain sounds trigger emotional or physiological responses that some might perceive as unreasonable given the circumstance. Apart from being very rare, misophonia is also one of the most troubling examples of synesthesia. It is a condition in which the synesthete experiences negative and aggressive emotional reactions to sound [13]. It has been described as a hatred of sound, with the most common triggers being human-related sounds, such as breathing, chewing and lip-licking [13]. The sounds that trigger this phenomenon are unavoidable, habitual sounds, which makes it even harder for synesthetes to live around people. It is crucial that synesthetes with misophonia receive cognitive behavioral therapy with the inclusion of background noise to mask the ‘annoying’ sounds.

Heredity in Synesthesia

While a proven genetic basis for synesthesia remains elusive, the phenomenon tends to run in families, as more than 40% of synesthetes report a first-degree relative with the condition [14]. Pedigree analyses have shown high transmissibility from parent to offspring, and each type of synesthesia is caused by a unique gene or set of genes [14]. In other words, even though genetic undertones impose a predisposition to synesthesia, it does not determine how the gene is expressed or what type of synesthesia the individual will experience. Indeed, individuals with one type of synesthesia are much more likely to have another as well, an observation that was made by
researchers Ramachandran and Hubbard as support for the idea that the defective pruning gene or genes confer a general propensity to linking unrelated sensations or even concepts. Furthermore, while individual synesthetes often display multiple forms of the phenomenon, large-scale factor analyses suggest that some variants co-occur with greater frequency within a single individual, suggesting that some forms are more highly related, which is suggestive of a common origin [14].

However, non-clustering forms still co-occur with greater frequency than predicted by prevalence rates in the general population, significantly impeding theories of single genetic markers and the notion of independence among different forms of the condition. Further research in examining the prevalence of synesthesia found a significant gender gap with a 6:1 ratio of female synesthetes to males, leading to the suggestion that synesthesia is an X-linked condition [6]. However, prevalence studies using random sampling have shown an even distribution of synesthesia among the genders, suggesting that the discrepancy was based on methodological flaws and self-report biases in earlier studies. In light of these conflicting results, research into the genetics underlying synesthesia remains in a nascent stage and will require much larger sample sizes and variants of the condition to understand the underlying factors for transmission.

Conclusion

In recent years, research has shown synesthesia to be a highly heritable phenomenon with numerous benefits to cognitive processing and memory. Synesthesia seems to occupy that mysterious boundary zone between elementary sensations on the one hand and higher-level abstractions on the other, intriguing scientists and providing an experimental lever for investigating high-level mental processes. To appropriately understand this condition with relation to normal cognition, future researchers must focus on both technically and intellectually diverse contributions from all areas of biology. Experiencing this unique phenomenon can give individuals a notable approach to life, which can work as both a blessing and a curse. Synesthetes often possess enhanced memory and creativity, making them excellent artists, musicians, and writers. However, they can also struggle with traditional schooling or experience ridicule from their family or peers. Thus, it is crucial for us as a society to not only encourage further research on the topic but also to promote awareness and acceptance of synesthesia.

References


Stress: An Overview

Rucha Kamat

Introduction

Stress can be defined as an emotional state in response to certain triggers that are perceived as exceeding a person's coping skills and available internal and external resources [1]. From time to time, it is common for people to experience stress. Stressors vary from person to person, so an event that one individual may perceive as stressful may not appear stressful to another. Likewise, the ability to cope with stress also differs based on the individual's perception. This article will discuss changes occurring in the brain while experiencing stress, symptoms of stress, and solutions to manage stress.

Stress-Induced Neurological Changes

As soon as a stressor is experienced by an individual, the sympathetic adrenal-medullary (SAM) system and the hypothalamic-pituitary-adrenal (HPA) axis are activated [1]. This activation brings physiological changes in the body preparing it to deal with stress [1]. The activation of the pituitary-adrenal axis releases adrenocorticotrophic hormone (ACTH), which is controlled by the corticotropin-releasing factor (CRF) present in the hypothalamus, being released in response to various stressors. The release of ACTH, which is a polypeptide tropic hormone, from the anterior pituitary subsequently triggers the liberation of adrenal steroids [2]. The CRF level decreases when the stressor is no longer present. “Activation of the stress system leads to behavioral and hormonal changes that improve the ability of the organism to adjust to homeostasis and increase its chances of survival [2].” Whether stress is acute or chronic depends on the duration of exposure to the stressors. “Chronic stress increases the length and volume of CRF in areas of the brain associated with fear and emotion, including the amygdala [2].” The stress-responsive systems are interconnected. For example, the activation of the HPA axis is facilitated by stress-induced norepinephrine (NE) release in certain regions of the brain such as the hippocampus and amygdala [2]. Since the brain tissue is made up of large amounts of polyunsaturated fatty acid, it is vulnerable to free radical attacks [2].
Neurotransmitters and Stress

When experiencing stress, neurotransmitters are also heavily affected. Neurotransmitters are chemical messengers in the nervous system that are responsible for controlling the ability to respond by perceiving, feeling, thinking, moving, acting, and reacting [1]. Gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, contributes to motor control, vision, and many other cortical functions [2]. “Stress induces the release of CRF and GABA from the amygdala and hypothalamus [2].” Dopamine, a neurotransmitter involved in the regulation of bodily movement, thought processes and rewarding sensations is also affected when experiencing stress [1]. “Stress-induced changes in dopamine (DA) levels within terminal areas seem to involve mainly ventral tegmental area projecting cells [2].” Acute stress produces stress-induced analgesia, which depends on the activation of dopamine (DA). Prolonged (chronic) exposure to stress, however, eliminates this response, resulting instead in a state of stress-induced hyperalgesia [3].

Norepinephrine (NE) is a neurotransmitter involved in learning, memory, and regulation of sleep, and also a hormone manufactured by the adrenal glands [1]. Stress has been reported to increase the release of NE in the brainstem, as well as in the hippocampus [2]. The brainstem is heavily involved with physiological responses to stress and panic. NE activates the amygdala, best known for its function of processing fear, and enhances the long-term storage of emotional memories in the hippocampus [2]. Serotonin is a neurotransmitter involved in sensory perceptions, sleep, and emotions. [1]. A significant reduction in serotonin levels increases the responsiveness to stress. “The 5-hydroxytryptamine receptor 1A (5-HT1A) receptors are down-regulated in distinct brain regions including the hippocampus and cortex following stress [2].” Among the neuroanatomical regions of

Figure 1. Schematic representation of neurotransmitters in the stress response system [2]
glutamatergic afferents to the Paraventricular nucleus (PVN), the dorsomedial hypothalamic nucleus is the candidate locus for glutamatergic neurons that could be activated by immobilization stress.

**Effects of Stress**

Although some stress is positive and necessary for humans to experience and grow out of their comfort zone, too much stress has substantial consequences. Chronic stress induces maladaptive neuroendocrine responses, which may lead to disturbances in growth and development, and may lead to vulnerabilities causing psychiatric, endocrine, metabolic, and/or autoimmune diseases [2]. Exposure to stress represents an important factor for a number of neuropsychiatric disorders such as depression, post-traumatic stress disorder, and other anxiety disorders. Even the neuroanatomical changes such as atrophy and loss of neurons in limbic and cortical brain regions are known to be associated with chronic stress. Chronic stress induces cognitive dysfunction in psychiatric patients, which leads to the loss of synaptic connectivity and neuronal networks in limbic brain structures including the hippocampus and cortex. “Oxidative stress contributes toward neuronal degeneration in the central nervous system in the process of aging as well as neurodegenerative diseases [2].” Chronic activation of the stress system may increase visceral adiposity, decrease lean body (muscle and bone) mass, and suppress osteoblastic activity. As a response to chronic stress, the adrenal gland continues to secrete cortisol increasing its concentration in the body, leading to hypercortisolism. Stress-induced hypercortisolism increases the risks of cardiovascular events increasing the mortality risk of affected subjects by 2-3 fold and curtailing their life expectancy by several years [4]. Stress has also been associated with impaired immune function and increased susceptibility to infectious diseases.

**Solutions**

There are a number of ways to cope with stress. Dietary macronutrients, namely β-carotene, vitamin C, and vitamin E, contribute to the antioxidant defense system. Non-pharmacological techniques, including meditation and yoga, are also a method of stress-relieving having greater effectiveness and no associated side effects [2]. Nowadays, there are even numerous apps for managing stress, namely Breathe2Relax, Mindfulness Coach, Virtual Hope Box, and PTSD Coach which provide deep breathing exercises, voice-guided meditation sessions and relaxation techniques to help cope with stress [5]. Anti-stress medications and treatments, such as the use of herbs, have been very common among Indian and Western Societies [2]. Pharmacological treatments include 5-HT1A receptor agonists, which are related to emotion and can induce anxiolytic and antidepressant effects. Buspirone, a partial 5-HT1A receptor agonist, is a non-benzodiazepine anxiolytic agent. The role of benzodiazepines like Alprazolam, Lorazepam, Clonazepam has been well documented in stress disorders such as anxiety, insomnia, adjustment disorders, and panic disorders. Cyclooxygenase inhibitors, specifically prostaglandins, also play an important role in mediating the HPA responses to immune insults [2].

**Conclusion**
Stress is experienced by many individuals on a daily basis. Stressors can trigger multiple neurobiological and neuroendocrine changes impacting multiple bodily systems and increasing risks of chronic conditions. The best strategy to prevent stress is by strengthening internal resources through yoga, meditation, and building strong coping skills. Pharmacological treatments are also available to reduce symptoms of stress-induced disorders.

References


Prion Diseases: Creutzfeldt-Jakob Disease

Yash Kilam

Introduction

Creutzfeldt-Jakob Disease (CJD) is the most common of a rare group of neurodegenerative pathogens known as human prion diseases [7]. Many researchers believe these diseases are caused by the development of abnormal bundles of proteins found on the surface of brain cells, called prions [5]. Despite being the most common form of a human prion disease, there are only an estimated 350 cases of Creutzfeldt-Jakob in the US per year [1]. Unfortunately, the disease has no known cure and is fatal, leaving most patients dead after anywhere from 4 months to 2 years following their first symptoms [6]. This article aims to look into the causes, details on diagnosis, symptoms, and treatments for CJD.

History

The disease was first discovered in the 1920s by German neurologists, Hans Gerhard Creutzfeldt and Alfons Maria Jakob [12]. CJD captured the public’s attention in the 1990s when individuals in the United Kingdom developed a variant of Creutzfeldt-Jakob disease, vCJD, upon eating meat from diseased cattle. However, the non-variant form of CJD has not yet been linked to infected beef [3].

Causes and Transmission

CJD is a rapidly progressive and invariably fatal condition [2]. The prion proteins behind it are misfolded isoforms of cellular glycoproteins which come together to become a singular particle: a prion [2]. There are three forms of CJD which one can contract: (i) Sporadic; (ii) Familial; and (iii) Acquired [4]. Sporadic CJD has no known cause and can occur naturally in anyone [4]. It represents over 85% of all cases of CJD and usually affects those above the age of 40 [6]. Familial CJD occurs when a mutation in the PRNP gene
for the \textit{PrP} \textsuperscript{C} \textbf{protein} causes normal \textit{PrP} \textsuperscript{C} to change into a disease-causing prion [9]. It accounts for 5 to 15\% of cases and occurs at a younger age than the sporadic form [6]. Acquired CJD happens when one comes in contact with infected material/tissue [4]. No confirmed cases of Acquired CJD have been previously reported [6].

\textbf{Diagnosis}

The only method to confirm a diagnosis of CJD is by performing a brain biopsy, which is very risky to execute while the patient is still alive [9]. If trying to narrow down the list of possibilities, a neurologist would start by carrying out a series of tests to make sure it isn’t misdiagnosed as a condition with similar symptoms, such as a brain tumor, Parkinson’s, or Alzheimer’s [10]. These tests may include an \textit{MRI} brain scan, an \textit{EEG}, a prototype blood test, a tonsil biopsy, or a genetic test [10]. Another examination involves a lumbar puncture, which can test spinal fluid to rule out other causes of dementia (a symptom of CJD) [9]. It can also show if there is an infection or increased pressure in the central nervous system [9]. If detectable 14-3-3 proteins are leaking into the spinal fluid, a sign of rapid neuronal degeneration, there is an increased chance that the person has CJD [9]. During a brain biopsy, a surgeon drills a tiny hole into the skull and removes a small piece of brain tissue using a very thin needle [10]. It is performed under general \textit{anesthetic}, meaning that the patient will be unconscious during the procedure [10]. Since a brain biopsy carries the risk of causing seizures, it is only performed in a small number of cases when there is no concern that someone may have CJD but rather, some other treatable condition [10].

\textbf{Symptoms}

Creutzfeldt-Jakob disease is marked by rapid mental deterioration, usually within a few months [3]. Symptoms include personality changes, anxiety, depression, dementia, impaired thinking, blurred vision or blindness, \textit{insomnia}, difficulty speaking, difficulty swallowing, and sudden jerking movements [3]. As the disease progresses over time, the patient’s mental symptoms will worsen [9]. Most infected individuals will eventually go into a coma [9]. Heart and respiratory failure, \textit{pneumonia} or other infections are generally the cause of death in CJD infected people [3]. For those with the rarer vCJD, psychiatric symptoms may be more prominent in the beginning, with dementia developing later in the illness [3].

\textbf{Treatments}

There is no treatment that can slow or stop the neuronal destruction caused by Creutzfeldt-Jakob disease and other prion diseases [7]. Many drugs have been tested, including acyclovir, amantadine, antibiotics, antiviral agents, interferon and steroids, although none have shown positive results [8]. Currently, the treatment for CJD aims to ease symptoms and make the person as comfortable as possible [1]. The drugs clonazepam and sodium valproate may help relieve \textit{myoclonus} [8]. Muscle stiffness and twitching may be treated with muscle-relaxing medications or antiepileptic drugs [7]. In the later stages of the disease, individuals with Creutzfeldt-Jakob disease will become completely dependent on others for their daily needs and comfort [7]. As of now,
researchers at the UCSF Memory and Aging Center are trying to identify compounds for a treatment or a cure for CJD and other diseases caused by infectious prions [8].

**Glossary**

- **Isoforms** - Proteins which have similar functions but their amino acid sequences are not completely the same
- **PRNP** - A gene which is used in the development of prion proteins on the surfaces of brain cells
- **PrPC protein** - The name of the prion protein controlled by PRNP
- **MRI** - A medical imaging technique used to form pictures of the bodily anatomy
- **EEG** - A method used to record electrical activity in the brain
- **Dementia** - A condition affecting memory, thinking and social abilities severely enough to interfere with your daily life
- **14-3-3 proteins** - A family of proteins which manage various cellular processes
- **Anesthetic** - A substance that induces insensitivity to pain
- **Insomnia** - A sleep disorder that is characterized by difficulty falling and/or staying asleep
- **Pneumonia** - An infection that inflames the air sacs in one or both lungs
- **Myoclonus** - A sudden, involuntary muscle jerk, shake, or spasm

**References**


Guillain-Barré Syndrome and Acute Canine Polyradiculoneuritis

Felissa Wallace

Abstract

Over the past few decades, scientists have discovered that canines can suffer from some of the same diseases as humans. The discovery of this phenomenon has led to the connection that human diseases that appear in canines could be treated with the same human treatment regimen. The same is true of neurological conditions that appear in both humans and canines. One such condition is called Guillain-Barré syndrome (GBS) in humans and idiopathic polyradiculoneuritis or acute canine polyradiculoneuritis (ACP) in canines. Both conditions are caused by the immune system targeting gangliosides. Even though both conditions are comparable, the treatment for the condition differs between species due to a lack of canine plasma. Within the past decade, there has been an increase in canine blood banks that could lead to treatment for ACP to be the same as GBS’s treatment.

GBS Background

Guillain-Barré syndrome (GBS) is a non-contagious, rare neurological condition that results from an immune response to an infection that mistakenly targets nerve tissue through a production of antigens. GBS has fewer than 20,000 cases a year in the US [1]. Cases occur in both sexes but it occurs more frequently in men; GBS can occur at any age, but mostly occurs in people who are older than 50 [1]. This rare condition is caused by a variety of common things, such as influenza or food poisoning.

Causes of GBS (Autoimmune)

Although the exact cause of all cases of GBS is unknown, in most cases, the immune system attacks the myelin sheath (an insulating layer made...
up of proteins and fatty tissue that surrounds nerves and axons) and damages it [Figure 1] [2]. The immune system's attack on the myelin sheath may also damage the axon (also called nerve fibers; their function is to transmit electrical signals from one neuron to another neuron) that is surrounded by the myelin sheath [3]. Damage to the axon makes the nerve unable to transmit signals to the muscles from the brain [1].

**Causes of GBS (Infection)**

In other cases of GBS, researchers found that GBS is caused by the immune system producing antibodies that target the peripheral nervous system—the network of nerves located outside of the brain and spinal cord [1]. More specifically, the immune system targets gangliosides, which are sialic acid-containing glycosphingolipids that cover cell membranes and contribute to cell differentiation in nerve bodies and axons located in the peripheral nervous system [5]. The immune system produces antibodies to target gangliosides because immune cells mistake the gangliosides cell membrane markers as the markers on the antibody. The markers on the pathogen help the immune system identify the pathogen as a foreign object that needs to be removed. A study has found that glycosphingolipids that make up gangliosides, are mostly found in the peripheral nerves and extraneural tissue and play a role in the development and signalling of muscles [6].

**Symptoms of GBS and Treatment**

The targeting of gangliosides by the immune system, causes the symptoms of GBS—which begins with a tingling or numbing of the limbs and progresses into muscle weakness and, in rare cases, paralysis. Most people with this condition recover within a range of a few weeks to a few years, but patients who recover continue to suffer from permanent nerve damage [7]. GBS is commonly treated with plasma exchange or immunoglobulin therapy.

**Background ACP**

Idiopathic polyradiculoneuritis or acute canine polyradiculoneuritis (ACP) is a condition that develops when a canine's immune system attacks nerves, causing weakness of the back legs, and then it quickly moves to the front legs, causing a crouched gait and potentially leading to paralysis. Similar to GBS, ACP can be triggered by a variety of things but is most commonly caused by an infection due to a raccoon bite [8]. This condition rarely occurs once a dog has been vaccinated.

**Causes of ACP**

In ACP the immune system targets ganglions, and leads to symptoms similar to GBS such as loss of muscle function and loss of nerve function. ACP also leads to inflammation which affects the motor nerves (the group of nerves that activate the muscles). Researchers hypothesize that some cases of ACP, can be caused by the infection of the immune system attacking bacteria that have chemicals on its surface that resemble gangliosides on nerve bodies surface [9].
**Treatments and effects of ACP**

Most cases of ACP are treated using supportive care that includes physical therapy and nutritional support because canine treatment for autoimmune conditions are not as advanced as a treatment for autoimmune conditions in humans [8]. Most dogs with ACP recover within a few weeks or months but continue to suffer from lasting nerve damage, similar to people who recover from GBS. Severely infected dogs may be able to move or lift their head and have a sensitivity to touch or possible respiratory failure [8]. Although both ACP and GBS are autoimmune conditions, researchers have found that immunosuppressants do not help to improve GBS and advise against treating GBS with immunosuppressants. This information was used to advise against treating ACP with immunosuppressants, even though there is no research on treating ACP with immunosuppressants [8].

**Similarities and Connections**

Although there is currently more research on GBS than ACP, researchers can use findings from GBS to further ACP treatment and understanding. Current ACP treatment could be improved by replicating or creating similar treatment based on GBS treatment. Not only do humans and dogs have similar immune systems, but veterinarians base treatment for ACP on research studies about treatment for GBS. Studies have found that “when comparing rodents' and dogs' immune systems to humans, canines’ immune system development shares more similarities to humans’ immune systems than rodents” [10]. Despite the fact that veterinarians base treatment regimens for ACP on the currently available treatments for GBS, veterinarians cannot replicate all of the treatments because the resources needed are not as readily accessible for canines as they are for humans. For example, the first canine blood banks were not established until 2010 [11]. After canine blood banks were established, months later plasma transfusions treatment capabilities for canines became a possible treatment method. [11]. Veterinarians can use the relatively new plasma therapy for canines to treat ACP, especially as plasma therapy is an effective treatment for GBS. They can even further separate the plasma to create immunoglobulin therapy for canines.

**Conclusion**

Although there is no cure for GBS or any treatment for anti-ganglioside antibodies, current treatments for GBS can be used to create an improved treatment for ACP. This possible improvement in ACP treatment could help further neurological research and studies that explore neurological diseases that appear in both dogs and humans. By using human treatments for human diseases that appear in canines, veterinary medicine could be revolutionized.

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References


Life With No Pain: Congenital Insensitivity to Pain

Gasser M. Alwasify

Abstract
Pain is mostly associated with unpleasant feelings and is largely despised and feared due to the emotional distress of sensations. However, without pain, humans wouldn't be able to separate harmful actions from non-harmful ones and wouldn't let their body heal. The sensation of pain is very crucial to the human body as it acts as a defense mechanism by alerting the body of on-going damage to the tissue or potential damage. The importance of pain is even more obvious when diagnosing patients with congenital insensitivity to pain, as their life is filled with terror of being hurt but being unable to detect it, which could ultimately lead to their death. This article dives into this disorder and how it can affect the normal daily lives of human beings, further revealing the vital importance of pain.

Background

According to the International Association for the Study of Pain, “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” It is very vital that scientists started considering it as ‘the sixth sense’ [1]. Pain serves a critical survival purpose: it protects our body from risky or damaging situations by prompting it to withdraw and escape these situations. For instance, if a person touches a hot object, a potentially endangering situation, he/she would displace their hand immediately as an attempt to reduce the damage caused by it. Furthermore, pain helps protect that part of the body after the incident. It informs the brain that this part of the body is damaged and requires time to recover. Therefore, the sensation of pain would alert that person to avoid utilizing it for a while, thus speeding up healing. The final function of pain is pretty straightforward: it helps humans learn to prevent similar damaging situations in the future [1].

When people understand that this sensation is just a neat way for the human body to indicate dangers, it can help to remove some of the worries that often accompany the pain. However, humans should never ignore pain. Unlike an alarm that can be turned off, pain should
not be overlooked as it can lead to hazardous consequences such as permanent tissue damage and potential permanent loss of function.

Before trying to comprehend the mechanism of pain, it is essential to understand the difference between pain and nociception. Pain is the state of agony usually followed by an injury, however, nociception is the subconscious detection of actual or likely tissue damage. Although they might seem very closely related at first, they can occur independently from each other. For example, some people with severe tissue damage might report having no pain or vice versa. Those are believed to be experiencing nociception, but no actual distresses of pain [2].

**Mechanism**

Pain occurs when special fibers called nociceptors respond to stimuli that can potentially cause tissue damage. Nociceptors are different from the usual neurons as they have a cell-like body with a peripheral axon and an ending that responds to diverse stimuli and is additionally the transmitter of the pain-related information to the central nervous system as shown in the figure [3]. Various discrete nociceptors respond to different stimuli like thermal, mechanical, and polymodal nociceptors. Thermal nociceptors mostly respond to heat or cold stimuli and notify the body about it, while the mechanical nociceptors are activated by sharp pinprick-type stimuli. Polymodal nociceptors are responsible for responding to any stimuli that are already causing tissue damage, leading to a slow-burning type of pain [5]. These nociceptors are the same receptors that also respond to chemicals released in chilly or spicy food like hot pepper, which induces a burning sensation [6].

C-fibers, characterized by unmyelinated axons, are the most abundant subclass of nociceptors, conducting slowly and responding to noxious thermal, mechanical, or chemical stimulation arising from neural crest cells. After the C-fibers, the second most abundant subclass of nociceptors are the thinly myelinated nociceptors that are characterized by their fast conduction and are more likely to convey more sudden pain [3].

When tissue damage occurs, it triggers the release of different chemicals at the site of damage, causing inflammation. Some of these chemicals are Prostaglandins, which enhance the sensitivity of receptors to tissue damage, making humans feel pain more intensely. When those receptors are activated, they transmit an impulse to the brain. The signals travel up the spinal cord
and reach the brain, which then processes the information and assesses how dangerous it is. Modern brain imaging has indicated that there is no specific area in the brain that processes pain. Instead, it is a complex array of reactions that take place in several parts of the brain which correspond with emotions, thought processes, etc. [6].

In this process, experience plays an essential role as it indicates if the stimulus was dangerous in the past or not. If the brain thinks that the event is dangerous or potentially damaging, it will evoke the sensation of pain and send impulses out to the peripheral cells that might compel that person to pull away or yell out in distress. Since pain is such a significant signal to the human being, it does not get subjected to the same kinds of filtering that occurs with the other senses. For instance, most senses will adapt to a stimulus that exists for a long time, and it starts to ignore it more and more over time, but in the case of pain, it is never neglected by the nervous system.

**Life with No Pain?**

Children and even young adults have always wished to have superpowers like not feeling pain ever and similar abilities. This is a very common thought for people as they think that feeling no pain would relieve them from the emotional distress that follows it. Nonetheless, this ‘super-ability’ is not fictional. This rare ‘super-ability’ has occurred in almost 20 cases, all over the world [7]. However, this isn’t something that people should wish for, as the inability to feel pain is extremely fatal and should never be considered as a ‘superpower’ but rather an exceedingly dangerous disorder.

Congenital Insensitivity to Pain (CIP), is a hereditary disorder where a person is not able to perceive any physical pain from birth. However, they can still feel touch and differentiate between sharp and dull objects, and hot and cold. On the other hand, they can’t sense if a hot object is burning their body. As described before, one of the most essential functions of pain is teaching the human brain that doing this action again might injure the body. Hence, patients with CIP cannot comprehend if certain actions are dangerous or not, it leads to the accumulation of wounds and broken bones due to a lack of awareness of the danger and not expressing any discomfort. This ultimately decreases these patients’ life expectancy. Most people born with this condition die during their childhood as they often do not realize their fatal injuries, such as broken bones until it is too late [1].

Recent research indicated that the prime cause behind this disorder is a gene mutation in different genes such as the PRDM12 gene, SCN9A, or the NTRK1 gene. Mutations more frequently occur in the NTRK1, the neurotrophic tyrosine receptor kinase 1 gene on chromosome 1, which is the receptor gene responsible for the nerve growth factor. In consequence, failure of differentiation and migration of neural crest cells occurs which induces the complete disappearance of small myelinated and unmyelinated nerve fibers causing the loss of pain sensation [8].

According to a study performed on a 1-year old with CIP, the most common symptoms accompanied by the insensitivity to pain are frequent episodes of fever, mental retardation, and
self-mutilating behavior. This specific child had the gene mutation in the PRDM12 gene, causing frequent tongue and perioral lesions, loss of teeth, and a habit of self-mutilation [8]. Moreover, self-mutilation such as frequent biting of the tongue, fingers, wrists, and feet is considered to be the most dangerous side-effect as it causes severe bleeding. This was evidently shown in a case documented of a 9-month-old boy, who suffered the aforementioned issue as he was reported with 3 months of prior self-mutilation. This further advances the idea that the dire effects of CIP only begin with the fruition of teeth in children as it permits them to hurt themselves through biting without awareness, resulting in scarring and deformation [9].

Unfortunately, there is no definite treatment for this disorder up until now due to the still largely unknown mechanism of pain perception and how such a disorder could cause the dysfunction of pain. However, alternative measures can be taken to help prevent self-mutilation and damage such as a new proposed mouthguard-like appliance that can prevent the biting. This appliance was applied extensively in a 16-month-old girl patient. Through several trials using different materials, the research found that the usage of methyl methacrylate for the mouthguard-like appliance proved to be successful as the 16-month-old girl accepted it and allowed her lesions to heal. It allowed her to enjoy a rather lesion-free life until she learned how to remove the appliance which gave rise to severe lesions and teeth loss. At that point, nothing could protect her from herself except her understanding of the situation and learning that removal of the appliance could injure her fatally [10]. One of the proposed solutions was full mouth extraction: the process of removing all the teeth in one’s mouth. The procedure was not agreed upon by the parents due to the psychological and functional implications.

These cases are nothing more than proof to demonstrate that congenital insensitivity to pain isn’t a blissful condition, but rather more of a curse to those who have it. A patient named Betz said, “People assume that feeling no pain is this incredible thing and it almost makes you superhuman. For people with CIP, it’s the exact opposite. We would love to know what pain means and what it feels like to be in pain. Without it, your life is full of challenges” [11].

References


Potential Benefits of Strychnos Nux Vomica in the Treatment of Parkinson’s Disease
Shambhavi Chaturvedi

Abstract
Parkinson’s disease, formerly known as “shaking palsy”, was discovered by Dr. James Parkinson in 1817. It is the second most chronic progressive neurodegenerative medical complication. No standard diagnostic criteria has been developed so far to define Parkinson’s in the clinical practice, and so the current diagnosis is based on the presence of cardinal manifestations, such as bradykinesia, rigidity, and tremor. To date, there is no potential cure for the disease, but several treatment approaches and therapies have been taken into consideration to provide relief from both motor and non-motor symptoms, but none could provide effective long term benefits. It has previously been proved through sundry cases that when different systems of medicines are combined, a patient’s health is drastically improved. As a novel approach to control the progression of the disease, the allopathic medications and surgeries can be combined with the traditional medicinal sciences like ayurvedic and homeopathic sciences. The article summarizes the potent neuroprotective effects of Nux vomica in the treatment of Parkinson’s disease.

Introduction
Parkinson’s Disease (PD), formerly known as “paralysis agitans” or“shaking palsy” is a chronic progressive neurodegenerative disorder of the Central Nervous System (CNS) which is caused as a result of damage to the basal ganglia cells of the human brain. The disease is characterized by a combination of symptoms, which include bradykinesia being the hallmark symptom of PD; cogwheel rigidity; resting tremor, and postural instability that can occur due to idiopathic reasons [1]. Other symptoms also include excessive drooling, shuffling gait, muscle
weakness, impaired speech, sleep disturbances, constipation, and liver damage. Additionally, some psychological symptoms such as abrupt mood changes like depression, apathy, hallucinations, confusion, delusions, and anxiety can be noticed in some patients. Dementia, which is caused by a significant loss of brain function, also represents one of the prominent symptoms when a patient reaches advanced stages of PD.

PD affects the basal ganglia, and its neurochemical origin was discovered in 1960 by O. Hornykiewicz, who showed that the dopamine content of substantia nigra and corpus striatum in post mortem brains of PD patients was extremely low, and was associated with a loss of dopaminergic neurons [2]. Later on, after elaborated studies, it was discovered that the neurons which extend from the substantia nigra to the putamen and caudate nucleus release the neurotransmitter dopamine (DA), which was degenerated in PD. The caudate nucleus of the basal ganglia contains neurons that liberate the neurotransmitter acetylcholine (Ach). Although the level of Ach does not change as the level of DA declines, the imbalance of neurotransmitter activity causes most of the PD symptoms [3]. The current treatment of PD is directed towards increasing the level of DA and decreasing the level of Ach. Since people with PD do not manufacture enough DA, taking it orally is useless as it cannot pass through the blood-brain barrier [3]. The article emphasizes the therapeutic significance of the strychnos nux vomica in the treatment of Parkinson’s disease.

Etiology of Parkinson’s Disease

To date, the cause of PD is unknown, but certain factors have been identified as the probable cause of this disease. These factors are categorized as genetic mutations, environmental factors, and pathogenic factors. It has been estimated that approximately 20% of PD cases are caused by genetic influences and mutations [17]. These cases could be associated with single-gene mutations and complex gene interactions with certain risk factors such as multiple gene mutations, gene-gene interactions, gene-environment interactions, and gene-epigenetic interactions. The idiopathic PD and the genetic PD cannot
generally be distinguished on clinical grounds, but the genetic PD human model can be used to study the idiopathic PD [17].

The pathogenic factors in PD include oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammation, protein aggregation, and apoptosis [15]. There is evidence that, in the brain, each of the above-mentioned processes is taking place and is involved in pathogenesis, but there is no evidence regarding which one comes first and in which order these processes take place. Additionally, all the attempts that have been made to influence the course of the disease by blocking one of these strategies have failed so far. Each of these factors act together in a network, so interference with any one of them is not sufficient to be able to provide neuroprotection [16]. This network of events leads to cell death and it is believed that the apoptotic cell signaling plays an important role in the death mechanism. This can also be a secondary phenomenon but the real mechanism of why cells die still remains unknown [16].

Some studies reveal that PD may also be induced by drugs like halogenated phenothiazines, chlorpromazine, promazine, mepazine, methoxyprazine, triflupromazine, pimozide, triperidol, haloperidol, reserpine, procaine, methyl dopa, and tetrabenazine. Additionally, toxic environmental chemicals such as herbicides, pesticides- paraquat, rotenone, organochlorine pesticides, organophosphates, chlorinated solvents, cyanide, methanol, carbon monoxide, metals- manganese, lead, iron, polychlorinated biphenyls, air pollution and particulate matter, and previous mild to moderate head injuries can also lead to symptoms of PD [19][21]. New light was thrown on the possible etiology of PD by a chance event. In 1982, a group of young drug addicts in California suddenly developed an exceptionally severe form of PD, and the cause was traced to the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which was a contaminant in illegal preparation of a heroin substitute. MPTP causes irreversible destruction of nigrostriatal dopaminergic neurons in various species and produces a PD-like state in primates [2]. These cases were then classified under the category of drug-induced Parkinson’s and are potentially reversible conditions when offering agents are removed. However, this may take a year or longer to resolve.

**Current Treatment Approaches**

The current pharmacological approach to treat PD is based on the concepts of symptomatic therapy (i.e. to control the symptoms of the disease.) Doctors usually recommend combinations of various supportive therapies like physiotherapy, occupational therapy, and speech-language therapies. They may also recommend lifestyle changes and may advise patients to go to speech-language pathologists to improve their speech difficulties [4].
One of the milestones of dopaminergic treatment was first achieved in 1961 when a human patient experienced levodopa infusion and oral levodopa replacement therapy. In 1968, levodopa was approved for PD patients as it could provide partial relief from the motor complications being a DA precursor, but it failed to slow down the progression of the disease. Later on, different potential drugs were discovered to slow down the progression of the disease similar to DA agonists (pramipexole, rotigotine), glutamate antagonists (amantadine), catechol-o-methyltransferase (COMT) inhibitors (entacapone or tolcapone). Monoamine oxidase B (MAO-B) inhibitor selegiline and rasagiline are also known to improve brain functions upon administration. Some studies revealed that when PD patients were administered selegiline in their early stages, they showed 35% better motor functioning [19].

Modern approaches include Deep Brain Stimulation (DBS), a prime non-destructive surgical treatment that involves implanting electrodes in specific brain areas. Other novel treatment approaches include cell replacement therapies using stem cell technology, gene introduction, gene replacements and substitutions to provide long term benefits to patients.

Potential Benefits of Strychnos Nux Vomica

Understanding the cause and mechanism of cell death is one of the most important aspects of trying to develop a neuroprotective drug that could slow down, stop, or even cure PD. Recently herbs and ayurvedic drugs have gained a lot of attention and consideration as potent neuroprotective agents to treat complex neurodegenerative disorders like Parkinson’s and Alzheimer’s. Strychnos nux vomica, also known as nux vomica, poison nut, semen strychnos, and quaker buttons, is a deciduous plant native to the Malabar Coast in Southern India and other Southeastern Asian countries like Sri Lanka and Indonesia. It is a major source of highly poisonous, intensely bitter alkaloid strychnine, brucine, and loganin and is derived from the seeds inside the tree’s round, green to orange fruit. However the medicinal properties of nux vomica are substantially due to the abundance of alkaloids strychnine and brucine [14] [20]. Strychnine is a highly toxic, colorless, bitter, crystalline alkaloid used as a pesticide, particularly for killing small vertebrates such as birds and rodents [6]. When inhaled or ingested at a higher dose through the eyes or mouth, strychnine causes poisoning which results in muscular convulsions and eventually death through asphyxia. Strychnine binds to Aplysia californica, Ach binding protein, and is a homolog of nicotinic receptors with high affinity and low specificity and does so in multiple conformations [7].

Nux vomica is used in some traditional medicinal systems that prevailed in India and China. The drug was previously used for the treatment of health conditions like allergies, back pain, constipation, common cold, stress, hemorrhoids, menstrual pain, headaches, flu, and digestive troubles. The alkaloid in nux vomica, strychnine, is a nerve tonic and stimulant, capable enough to affect the functioning of both the developing and the mature nervous tissues. It acts as an antagonist of glycine and Ach receptors. Through various studies, it has been revealed that it primarily affects motor nerve fibers in the spinal cord that control the process of muscle contraction. In order to generate an impulse, excitatory neurotransmitters must bind to their
respective receptor of the nerve cells. However, in the presence of inhibitory neurotransmitters, the process of generating the action potential becomes difficult. Therefore, a greater concentration of neurotransmitters is required to bind to the receptors in order to generate the needed potential. In PD, due to the loss of dopaminergic neurons, their level in comparison to Ach reduces and this causes Parkinsonism symptoms. Strychnine, upon administration, can antagonize Ach and glycine (inhibitory neurotransmitters) and bind non-covalently to their receptors to prevent the postsynaptic neuron from inhibitory effects of glycine. Therefore action potentials can be triggered with lower levels of excitatory neurotransmitters. The use of nux vomica can prove to be beneficial in the management of the response fluctuations of levodopa and DA agonist therapies. The response fluctuations like honeymoon, wearing OFF, ON-OFF fluctuations, delayed ON, NO-ON phenomenon (dose failure) are commonly seen in the advanced stage PD [18]. At such stages, medication therapies fail to control the fluctuating motor symptoms and dyskinesia. Thus the patient becomes very vulnerable and they often die due to infections and other medical complications. The aim of therapies at this stage is optimal symptom control and they can be improved using herbal medications like nux vomica.

**Pharmacokinetics of Nux Vomica**

The administration of strychnine is carried out orally, by inhalation or systemic (via injection) routes. It is a potentially bitter substance and hence, on the administration to humans, it activates bitter taste receptors TAS2R10 and TAS2R46 [8]. Strychnine is rapidly absorbed from the gastrointestinal tract [9]. Due to the slight protein binding, it leaves the bloodstream quickly and distributes it in the tissues [10]. It has been recorded that approximately 50% of the ingested strychnine dose can enter the tissues within 5 minutes [6]. The drug is actively transported by plasma and erythrocytes. It is rapidly metabolized by the liver microsomal enzyme system requiring NADPH and oxygen [6]. The biological half-life of strychnine is about 12 hours [14]. After a few minutes of ingestion, strychnine is excreted, unchanged in the urine, and accounts for about 5-15% of the sub-lethal dose given over 6 hours. Excretion or elimination follows first-order kinetics and is virtually completed in 48-72 hours [11] [14].

**Toxicology**

Nux vomica is a widely known herbal medicine used to treat a wide range of medical complications including cancer. The prime concern with the use of the drug is its toxicity. The toxicological studies of nux vomica have revealed that strychnine is highly toxic to humans and animals. Poisoning by inhalation, swallowing, or absorption through eyes and mouth can be fatal. The deaths of individuals after Strychnine nux vomica administration is primarily caused by respiratory arrest. The other possible causes of death include cardiac arrest, multiple organ failure, or brain damage. Despite being used to treat severe diseases and disorders, the toxicity of strychnine is not ethically studied by researchers worldwide, and thus the plant appears on the commission E-list of unapproved herbs because it has not proven to be safe or effective.
All its medical and toxicological effects have been well studied in the traditional Indian medical system, Ayurveda. The Ayurvedic science is based on the fundamental principle known as the “Panchamahabhuta Siddhant,” which states that all material forms, including the body, are composed of 5 subtle elements: Prithvi (Earth), Jala (Water), Vayu (Air), Agni (Fire), and Aakash (Space). The “Tridosha Theory” establishes a relationship between these five elements. “Dosha” is an ayurvedic term used to describe an individual’s inherited traits and tendencies. In simpler terms, dosha means impurity, and an imbalance in dosha can result in diseased states or conditions. The “Tridosha Theory” explains the relationship of these elements as 3 Dosa-

a) Vata - air and space: movement of air and the space within the body
b) Pitta - fire and moisture: transformation, moisture, and energy within the body
c) Kapha - earth and water: strength (immunity) within the body

In Ayurveda, a drug called hudar has been identified as a mixture containing Strychnos nux vomica. The seeds used in the treatment are first immersed in water for five days and then immersed in milk for the next two days, followed by boiling in milk [12]. Through this approach, the toxic content can be lowered and then it can be considered safe and effective and is recommended for its use. The Ayurvedic studies of the drug reveal that it is a Vatashaamaka (i.e. it alleviates the Vata-Tridosha concept of Ayurveda and reduces pain.) In addition, due to its sharp properties, hudar stimulates and strengthens the nerves and is useful in treating various disorders, including neuralgia, facial palsy, hemiplegia, paralysis, insomnia, epilepsy, diabetes, anemia, constipation, chlorosis, spermatorrhea, and other infections. The lethal dose of hudar in humans is about 30-120 mg, and an overdose can lead to intoxication and convulsions [13][14].

**Conclusion**

Parkinson’s disease is a chronic, progressive neurodegenerative disorder caused by the degeneration of the dopaminergic neurons in the substantia nigra pars compacta of the brain. Since the cause of the disease is unknown, the modern treatment approaches focus on symptomatic therapies. As a novel treatment approach, allopathic sciences can be combined with the ayurvedic and homeopathic sciences to develop potent neuroprotective agents. The ayurvedic studies suggest that there are several drugs that have an effect on nerve cells and which upon safe administration, can alter the progression of neurological disorders. Strychnos nux vomica is one such native herbal drug found in the tropical forest of the Malabar Coast in Southern India and Southeastern Asian countries. Recent studies reveal some neuropharmacological effects of the drug and have postulated it as a nerve tonic that might be useful in the development of neuroprotective drugs. Elaborated study on this herb, especially on the toxicological parameter, can give promising results with lesser side effects. This article summarizes the potential benefits of the herb and its use as a novel neuroprotective agent for the treatment of Parkinson’s disease combined with other systems of medicines.

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References
The Role of the Amyloid Precursor Protein Gene and Copper in Alzheimer’s Disease

Emily Barron

Abstract

Alzheimer’s disease has been described as the cognitive impairment of an individual due to the formation of senile brain plaques (SP), and neurofibrillary tangles (NFT) [2]. Researchers have hypothesized a multitude of possible causes for the pathogenesis of Alzheimer’s disease (AD), however strong evidence has been found suggesting that environmental factors influence the progression of AD. These environmental factors include, but are not limited to, exposure to metals such as aluminum, copper, zinc, selenium, manganese, and iron [9]. This paper will review the clinical literature regarding the intricate relationship between copper (Cu) neurotoxicity and the Amyloid Precursor Protein (APP) involved in AD pathogenesis.

Introduction

Alzheimer’s disease has been defined as the cognitive impairment of an individual due to the formation of senile brain plaques (SP), and neurofibrillary tangles (NFT) [2]. These defining features are regarded as the main pathological symptoms of Alzheimer’s disease since the first description of the disease by Alois Alzheimer in 1907 [2]. More specifically, Alzheimer’s disease is defined by the deposition of β-amyloid (Aβ) plaques, the accumulation of neurofibrillary tangles, and the loss of neurons and synapses in select areas of the brain, specifically the cerebral cortex [16]. Many patients with Alzheimer’s show unique variations in the persistence of these pathologies, thus creating difficulties in establishing a single theory for the causes of the disorder.
There are various hypotheses that researchers believe can explain Alzheimer’s disease; however, the exact cause of the disease’s progression is unclear. Possible causes are proposed to be (1) acceleration of aging, (2) degeneration of anatomical brain pathways, (3) environmental factors, (4) genetic factors, (5) a metabolic disorder resulting from mitochondria dysfunction, (6) vascular factors such as a compromised blood-brain barrier, (7) immune system dysfunction, and (8) infectious agents [2].

Although the acceleration of aging and brain degeneration are plausible hypotheses for the development and progression of Alzheimer’s disease, many researchers have found strong evidence in supporting the role of environmental factors in influencing the progression of Alzheimer’s. These environmental factors include exposure to various metals such as aluminum, zinc, copper, manganese, iron, and selenium [9]. There is a debate within the scientific community on whether or not metal toxicity appears in the brain as a result of Alzheimer’s disease, or if metal toxicity of the brain precedes the disease [8]. The increase in recognition of metal contaminant levels in the air, water, soil, sediment, and food has prompted researchers to distinguish the difference between “bioavailability” and “bioaccessibility” [12]. Metal bioavailability implies the presence or maximum amount of metal in ingested food, water, soil, or sediment particles that can be released during digestion [12]. Conversely, metal bioaccessibility is the ability of the ingested metals to be absorbed and transported across the intestinal wall and transferred into the bloodstream [12].

**Literature Review**

Researchers have hypothesized that inorganic copper ingested from drinking water, using copper plumbing, and using bioaccessible vitamin and mineral supplements containing the metal is a possible cause of Alzheimer’s disease [4]. Although copper is an essential organic element that is needed for energy production by the enzyme cytochrome c oxidase, ingesting inorganic copper can lead to metal dyshomeostasis in the brain, an imbalance or breakdown of the brain’s normal function [5]. Copper is an integral component of cuproproteins, and is required for many physiological functions, such as energy production, the scavenging of free radicals, connective tissue production, iron mobilization, and neurotransmission [13]. Researchers propose that Alzheimer’s disease could even be classified as a copper-overload disease much like Wilson’s disease, which is a copper metabolism disorder in the brain [5,3]. Research has shown that there is a link between the interaction of copper, the APP gene, and the acceleration of Alzheimer’s disease.

The APP gene, also known as the amyloid precursor protein, located on chromosome 21, was first identified in 1987 by laboratories independently using partial protein sequence information obtained by the Glenner and Beyreuther/Masters laboratories several years earlier [14]. APP processing generates the \( \beta \)-amyloid (\( A \beta \)) peptides, which are deposited as the amyloid plaques in the brains of individuals afflicted with Alzheimer’s disease (Figure 1) [16]. The liberation of \( A \beta \) from APP requires the action of \( \beta \)- and \( \gamma \)-secretases which process APP at amino-terminus and carboxyl-terminus of the \( A \beta \) sequence [16]. Point mutations and duplications of APP are causal for a subset of early-onset familial Alzheimer’s disease, and roughly 5-10% of Alzheimer’s cases are familial with an autosomal dominant inheritance of mutations in APP [16]. Point
mutations and duplications of APP can cause early onset of familial Alzheimer’s disease; however, although mutations in APP are found in rare cases, they are nevertheless important because they provide the necessary evidence that APP and Aβ play a central role in AD pathogenesis [14].

**Figure 1:** The process showing the creation of senile brain plaques from amyloidgenic pathways of APP processing [17].

**Analysis**

Although the literature concerning the role of the APP gene in Alzheimer’s disease is vast, there is also a large amount of research concerning the interaction between the APP gene and copper in relation to Alzheimer’s disease. APP molecules contain metal-binding sites for copper and zinc [15]. The activity of the copper-binding domain (CuBD) is unknown. However, it has been found that APP reduces Cu(II) to Cu(I) and this activity could promote copper-mediated neurotoxicity [15]. Cu(II) refers to copper in the 2+ oxidation state, while Cu(I) refers to copper in the 1+ oxidation state [1].

The expression of APP in the brain suggests that it could have an either a direct or indirect role in neuronal metal homeostasis [15]. Metal homeostasis in the brain is characterized as the appropriate amount of organic, bioaccessible metal needed for brain function and activity [11]. Conversely, metal dyshomeostasis is a disruption of brain function and homeostasis due to high amounts of metals in the brain [11]. It is believed that the relationship between APP and inorganic copper in the brain produces metal dyshomeostasis during Alzheimer’s disease [15]. In Alzheimer’s disease, the reduction of Cu(II) to Cu(I) by APP involves an electron-transfer reaction and could also lead to a production of hydroxyl radicals [10]. This could mean that the copper-mediated toxicity of APP-Cu(II)/(I) complexes may contribute to neurodegeneration in individuals with
Alzheimer’s disease [10].

In a case study done by Acevedo (2011), it was found that copper promotes APP trafficking in cultured polarized epithelial cells and neuronal cells (Figure 2). Previous research had demonstrated that copper increases the level of APP at the cell surface. The purpose of the research presented in this 2011 study was to show that out of the three most abundant trace elements found in the human body, namely iron, copper, and zinc, copper played the most influential role in relation to the APP gene [1]. The article clearly shows that iron and zinc had a minimal effect on the APP gene [1]. Researchers used live-cell imaging and endocytosis assays to study the relationship between copper and the APP gene [1]. In doing so, they found that increased copper promotes an increase in cell surface APP by increasing its exocytosis and reducing its endocytosis [1].

Figure 2: Images showing 5 μm of copper injected in the brain causes APP relocalization from a predominant perinuclear location to neurites, as indicated by the white arrows [1].

In SH-SY5Y neuronal cell lines and primary cortical neurons, the researchers found that copper promoted a redistribution of APP from a perinuclear localization to a wider distribution, including to neurites [1]. SH-SY5Y cells are a human-derived cell line that is often used as in vitro models of neuronal function and differentiation [1]. The findings show that copper modulates APP metabolism [1]. Furthermore, researchers found that a decrease in intracellular copper down-regulates the APP gene expression, and elevated cellular copper levels result in the up-regulation of APP gene expression [1]. It was also demonstrated that in both neuronal and non-neuronal cell models, APP traffics from the Golgi to intracellular compartments and the cell surface in response to increases in intracellular copper, but not zinc or iron [1]. This is potentially due to an increase in the rate of APP exocytosis with a concomitant reduction in its rate of endocytosis [1].

In another study by White and colleagues (1999), the direct or indirect role between copper, the APP gene, and neurotoxicity was examined. This was done by measuring copper, zinc, and iron levels in the cerebral cortex, cerebellum, and selected non-neuronal tissue from APP and APLP2 knockout mice using atomic absorption spectrophotometry [15]. The APLP2 gene is a member of the APP gene family and contains heparin-, copper- and zinc-binding domains at the N-terminus, BPTI/Kunitz inhibitor, and E2 domains in the middle region, and transmembrane and intracellular domains at the C-terminus [15]. The APLP2 gene is required to mediate neuromuscular
transmission, spatial learning, and synaptic plasticity [15]. A knockout mouse is a laboratory mouse in which researchers have inactivated or “knocked out” an existing gene by replacing it or disrupting it with an artificial piece of DNA [15]. Researchers used knockout mice and control mice which they labeled “wild-type” (WT) mice [15]. 

White (1999) suggests that the identification of zinc and copper metal-binding sites on the APP and APLP2 proteins suggest a possible role in biometal homeostasis. To test this, the levels of copper, zinc, and iron in the brain and other non-neuronal tissues of knockout mice and WT mice were measured [15]. They found that APP and APLP2 expression significantly and specifically lowers copper levels in the cerebral cortex of adult mice, as well as their liver [15]. The increased copper levels in the cerebral cortex and liver were not an artifact of the “knockout” procedure [15]. The knockout mice and the WT mice were of the same background, thus indicating the effect found is protein-specific [15]. This study is different from the study done by Acevedo (2011) because White (1999) explored the relationship between the APLP2 gene and copper as well as the relationship between the APP gene and copper. This was done because APLP2 also contains a copper-binding ectodomain. However, it was shown that APLP2 had a smaller effect than APP on copper levels in the cerebral cortex [15].

As copper has a high capacity to generate free radicals, even at low concentrations, copper metabolism must be tightly regulated to prevent tissue damage in the brain [15]. The study done by White (1999) provided valuable insight into the relationship between the APP gene, APLP2 gene, and copper by demonstrating that APP and APLP2 are involved in modulating copper but not iron or zinc. However, it is still not clear how this process occurs, or which tissues or fluids are the predominant site of interactions between copper and APP or APLP2 [15]. Cells in the brain and liver express relatively high levels of APP, and the release of cellular APP/APLP2 with bound copper may provide a means of removing excess copper from certain cell types [15]. Researchers explain that due to the highly conserved sequence homology of the CuBD between species, the results from this study show that it is very likely that APP has a similarly important role in copper homeostasis in humans [15]. The perturbation of this function could have important implications for disease initiation/progression since the cortex is commonly affected in patients afflicted with Alzheimer’s disease [15].

Conclusion

The aforementioned studies outline the relationship between copper and the amyloid precursor protein gene. More specifically, they have explored the relationship between the APP gene and copper in the brain, explained how the APP gene and copper affect the brain in an individual, and finally, they elaborate on the effects that those changes play in Alzheimer’s disease. The literature has shown that there is a direct relationship between the amyloid precursor protein gene and copper in various regions of the brain; however, it would be useful to conduct further research into this topic as it relates to Alzheimer’s disease.
New contextualization of the relationship between amyloid precursor protein gene and copper lies in broadening the scope of the research. Instead of continuing research into the relationship between the amyloid precursor protein gene and copper, it would be useful to research the relationship between the amyloid-beta protein (Aβ) and copper in the brain. This could be interesting since the amyloid-beta protein is a part of the amyloid precursor protein gene family. Taking this research into a more specific realm of understanding will be valuable to researchers trying to understand many of the unsolved complexities of Alzheimer’s disease. Additionally, it would be worth comparing and contrasting the relationship between various metals and the APP gene. Although articles such as White (1999) and Acevedo (2011) explore the relationship between copper, iron, and zinc with the APP gene, it would be beneficial and illuminating to research the relationship between aluminum and the APP gene. According to Fisher (2018), aluminum is thought to be highly influential in the progression of Alzheimer’s disease. The possibility of contextualizing the research being done with the APP gene and copper into an analysis regarding a new inorganic element may be useful for researchers attempting to understand Alzheimer’s disease. Furthermore, rather than simply researching the relationship between aluminum and the APP gene, research of this nature should also be done with other metals involved in Alzheimer’s disease such as manganese and selenium [7].

References


Looking into Criminal Minds: The Neurological Basis of Crime

Aarsha Shah

Abstract
Extensive research has been conducted that explains the neurological, genetic, and environmental factors that predispose individuals to criminal behavior. There are several critical differences in the brain scans of incarcerated versus non-incarcerated individuals [1]. The low-activity form of the MAO-A gene correlates with increased levels of aggression [2]. Abuse in childhood, both physical and psychological, is often seen in individuals demonstrating psychopathic tendencies [3]. These factors, along with others, allow us to determine individuals at risk of becoming criminals. However, there are ethical quandaries regarding the implications of this research on treatment and how accountable individuals should be held for their crimes.

Autonomic Functioning and Associated Theories

Heart rate and skin conductance are two psychophysiological measures that indicate how the autonomic nervous system functions. There is a proven association between lower autonomic functioning and increased anti-sociality and violence. For example, there are studies proving that a low resting heart rate in adolescence can be associated with an increased likelihood of becoming a criminal. There are several different theories that explain the relationship between blunted autonomic functioning and increased anti-sociality. The sensation-seeking hypothesis, for example, explains that individuals engage in antisocial behavior to increase arousal levels. On the other hand, the fearlessness hypothesis explains that antisocial individuals engage in criminal behavior because they do not experience the same physiological responses that the average individual does [4].

It is interesting to think about the way the average person responds to certain situations as opposed to individuals engaging in criminal behavior. On a fundamental level, we view and understand our environment differently. My next question was: could this be genetic?
Monoamine Oxidase A

Monoamine oxidase A, also known as MAOA, is a gene that codes for an enzyme responsible for breaking down monoamines, including serotonin, epinephrine, dopamine, and noradrenaline. These neurotransmitters regulate emotion, sleep, stress, among other important bodily functions [8]. There are several studies that prove a link between MAOA and aggression. Individuals possessing the low activity form of this gene (MAOA-L) tend to be more aggressive. Negative experiences affect them more, so they react more aggressively in defense. One study investigated the behavior of people when provoked. Results showed that MAOA-H individuals showed lower levels of aggression than MAO-L individuals [2].

Environmental factors also play a key role. In the study mentioned above, the level of provocation impacted the levels of aggression displayed by the subjects. For example, when the level of provocation was low, both MAO-L and MAO-H individuals reacted with similar levels of aggression. However, when the level of provocation was high, there was much more aggression displayed from MAO-L subjects. In another study, MAO-L individuals who were maltreated as children were accurately predicted to commit crimes. Though the MAOA gene correlates with aggressive behavior, it is clear that the environment is a factor to be considered, too [2].

After discovering possible genetic factors, it was clear that genetics was only part of the equation. I knew that there were specific sections of the brain that regulated things like behavior, emotions, and more. So I wondered: could disparities in these sections be another important factor?

Notable Studies

Brain scans of over 800 incarcerated men were reviewed in a research study that spanned over ten years, eight prisons, and two states. This study was conducted by dividing participants into groups based on what they were convicted of. Results indicated that those who attempted or actually committed homicide had reduced gray matter in their brains, especially in regions associated with social cognition, emotional processing, and behavioral control. According to Professor Jean Decety at UChicago, “More gray matter means more cells, neurons, and glia...That’s what you need to make computations, to process information – whether it’s emotional information that you use to feel empathy for someone else, or information that you use to control your behavior, to suppress your tendencies to react.” It is important to note that studies are still being conducted to determine if reduced gray matter is a causal factor of homicide; we have yet to gain enough evidence to prove this link [1].

Twenty-one people with antisocial personality disorder were examined. Compared to individuals with no mental disorders, the brain scans of these individuals (on average), showed an eighteen percent reduction in the volume of the brain’s middle frontal gyrus and nine percent reduction in the volume of the orbital frontal gyrus [5]. These structures are located in the frontal lobe, which controls important cognitive skills such as emotional expression, judgment, and more [7].
Dr. Helen Morrison, a forensic psychiatrist, studied and interviewed 135 serial killers. By doing this, she was able to discover many similarities between them. She believes that a chromosome abnormality that manifests itself around puberty may be the trigger for their violent behavior. Their brain scans show that they lack empathy toward their victims and that they never really develop a sense of belonging in the world [3].

A study conducted in 2009 compared the brains of psychopaths to the brains of non-psychopaths. Researchers discovered that in the psychopaths, the amygdala was deformed, there was a thinning in the outer layer of the cortex, and there was approximately an eighteen percent reduction in the volume of the cortex. As Adrian Raine, chair of the Department of Criminology at the University of Pennsylvania explains, “The amygdala is the seat of emotion. Psychopaths lack emotion. They lack empathy, remorse, [and] guilt...” [5].

It is clear that many different parts of the brain play a role in criminal behavior. But now that we have all of this knowledge, what is the next step? Can we move from simply learning to actually implementing solutions? But then, at what point does human interference become immoral?

**Ethical Considerations**

Many of the brain differences that typically lead to an individual becoming a criminal can be measured early in life. For example, criminologist Nathalie Fontaine studies tendencies toward being callous and unemotional (CU) in children ages seven to twelve. She explains that “CU traits can be used to identify a subgroup of children who are at risk,” but these traits can change as children grow. There is debate over the ethics of helping children who are at risk of becoming criminals. Experts are hesitant because brain procedures can be invasive and risky, and the individuals in question have not committed any crime. However, there are also non-invasive options. Fontaine’s studies show that emphasizing positive reinforcement instead of punishing bad behavior can make a difference. Raine is testing the impact of omega-3 fatty acids (fish oil) to see if it can reduce aggressive behavior in children. Because it is used in cell growth, it is possible that fish oil will help brain cells grow larger. Since it is relatively harmless, it is more likely to be accepted than surgical treatment [5].

Research also poses questions about accountability. For example, psychopaths know right from wrong, but they do not feel it the same way as the average individual. They did not choose to have a differently functioning amygdala, so what does that mean for how they should be punished? Or, with the MAO-A gene, individuals cannot control their genes, so how responsible should they be held for their actions? [5]

I believe that we should still hold criminals accountable for their behavior. Though genetics and brain composition do incline them to act in one way or the other, it does not force them to do
so. Furthermore, as the story of James Fallon proves, one can have all of the biological traits that make a killer but still take a different path.

**Why Environment Matters Too**

James Fallon is a neuroscientist who has been studying the brain of psychopaths for over twenty years. He explains that serial killers tend to have lower activity in the orbital cortex, the area of the brain involved with ethical behavior, decision making, and impulse control. When there is low activity here, there is less suppression of behaviors, which can include rage and violence [6] [3]. Fallon himself has the same low orbital cortex activity that he saw in serial killers during his research. Furthermore, he has the low-activity form of the MAO-A gene. Not only that, but he explains that psychopathic tendencies can be passed down from generation to generation, and there were many killers in Fallon’s lineage. However, he grew up to research killers, not to become one. According to Fallon, genes don’t determine your fate. Instead, they play a role in tipping you one way or the other. An important factor that was luckily missing in Fallon was abuse. Fallon grew up in a happy, non-abusive household [6]. Results of one study of fifty serial killers indicate that approximately seventy percent of them experienced maltreatment, and approximately fifty percent suffered from psychological abuse [3]. Thus, though patterns in one’s brain or genes can make them more inclined to behave a certain way, the environment is a major factor in determining what ends up happening.

In conclusion, though there are neurological, genetic, and environmental factors that may help tip the scales in a particular direction, there is no exact formula that will determine one’s likelihood of becoming a criminal with a one-hundred percent guarantee.

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**References**


Out-of-Body Experiences

Srikar Chintala

Abstract

Out-of-body experiences are events where an individual feels as if their “spirit” drifts away from their physical body which is simply left idle [1]. Many have characterized this event as “paranormal”. However, it has been discovered that out-of-body experiences can occur due to a misunderstanding between a portion of the brain, the temporoparietal junction, and the vestibular system, and this misunderstanding can occur to anyone, even an entirely healthy person.

Background

Out-of-body experiences. Does this sound familiar? How about a similar and popular concept of “astral projection”? If none of these sound familiar, out-of-body experiences are events where an individual’s “spirit” drifts away from their physical body which is simply left idle. Out-of-body experiences have been reported by millions of people all around the world. According to surveys, approximately 10% of the world’s population has experienced some form of these out-of-body experiences at least once in their lifetime [1].

Out-of-body experiences can vary drastically. Some have reported minor instances of a feeling that their brain and body are loosely connected, while others recount instances of them floating far from their body or even into different dimensions [1]. Professors such as Olaf Blanke state that these
experiences are a striking phenomenon because they challenge the existential idea and unity between the mind and body. Yet, only a few scientific investigations have attempted to study this concept because these experiences generally occur spontaneously and extremely rarely; once or twice in a lifetime [2].

However, within the last two decades, scientists have unlocked the mystery by explaining that the feeling that individuals feel is entirely real, but the idea of the “soul” genuinely leaving the body is false [3]. The concept can be entirely explained by science.

Explanation

One of the most well-known out-of-body experience experiments was conducted by Charles Tart, an American psychologist known for his work on consciousness, on a subject known as Miss Z, a young woman in her twenties who frequently had spontaneous out-of-body experiences. Miss Z was attached to an EEG machine and a five-digit code was placed on a shelf above her bed. She managed to self-induce an out-of-body experience on four days, but she did not claim to see the number on the first three nights. However, on the fourth night, she gave the number correctly. If this experiment was entirely true, it is possible that out-of-body experiences could be paranormal [7]. Yet, the psychologists Leonard Zusne and Warren Jones believed there was a possibility that the subject obtained the number through ordinary sensory means which was not ruled out during the experiment. For example, when light fell on the code it was reflected from the surface of a clock located on the wall above the shelf. The subject was not constantly observed and it was also suggested she may have read the number when she was being attached to the EEG machine [8]. It was also noted that if Miss Z attempted to climb up and look, there would be a pattern of interference in her brain-wave readings; that was exactly what it showed [9]. Hence, these experiences have nothing to do with paranormal activity.

Neurological evidence has expressed that these experiences are related to an interference with the temporoparietal junction, where the parietal lobe and the temporal lobe meet [2]. This area has many inputs from other parts of the nervous system. For instance, this area takes in inputs from the thalamus (which sends sensory information) and the limbic system (which is important in emotion and memory). Along with that, this area also takes in information from visual, auditory, and somatosensory (bodily sensations) systems. Since the temporoparietal junction integrates information from the external environment and within the body, it is thought to play a connection between one’s body and self; thus, the temporoparietal junction is the prime contender for the origin of out-of-body experiences [1].

Olaf Blanke, a neuroscientist at Ecole Polytechnique Fédérale de Lausanne, is considered by many as the scientist who has demonstrated that out-of-body experiences have a well defined scientific basis [4]. For instance, in one of Blanke’s studies in 2002, he electrically stimulated the temporoparietal junction in a patient being evaluated for epilepsy, and immediately after, the patient experienced a brief out-of-body experience [4]. To follow up with this theory, Blanke
studied six neurological patients with brain lesions that caused them to experience out-of-body experiences. Later, he found that the temporoparietal junction was involved in all of the patients [1].

In another study, researchers studied a patient who could have an out-of-body experience at will. They placed the patient under an MRI, and the MRI showed that there is a strong deactivation of the visual cortex. However, there was a strong activation of the left side of the brain, more specifically the temporoparietal junction [3]. The activation of the temporoparietal junction is what makes people feel that they are not a part of their body, and, instead, they are “floating around” their body.

Furthermore, another study in 2016 concerning the vestibular system was conducted by Christophine Lopez—a leading neuroscience at Aix-Marseille Université. She noticed that the vestibular system, specifically the inner ear, can also lead to out-of-body experiences due to its direct connection with the temporoparietal junction. The vestibular system is responsible for providing the body with a sense of balance and spatial orientation. If this system malfunctions, it can lead to the brain having a misunderstanding of one’s body and its relationship to the environment. Hence, it would lead to an out-of-body experience [6].

Although the idea behind how people are able to “see” themselves is not entirely clear, everyone has seen himself or herself through a mirror or such, and every individual has created fantasies in their head. Hence, it is not entirely difficult to believe that out-of-body experiences can cause people to feel “apart” from reality [1]. It can almost be expressed as a hallucination that one’s brain triggers automatically. Yet, as stated before, there is no scientific evidence to support the idea that a person’s consciousness can actually travel outside the body.

Causes

There are many factors that can cause an out-of-body experience. More specifically, researchers are aware that these experiences can be caused “by brain traumas, [dissociative diseases/disorders], sensory deprivation, near-death experiences, dissociative and psychedelic drugs, dehydration, sleep, and electrical stimulation of the brain, among others. It can also be deliberately induced by some.” [3]. So far, the reasons for why some of these causes can stimulate an out-of-body experience is unknown. However, it is extremely likely that these causes can stimulate a malfunction of either the vestibular system or the temporoparietal junction, leading to an out-of-body experience.

Yet, in one important study, Christophine Lopez states that out-of-body experiences were approximately three times more frequent in patients with vestibular disorders versus those without them. When the vestibular system becomes faulty due to vestibular disorders, the faulty vestibular system could send wrong signals to the brain about the person’s motion. Then, it is possible that the conflicting information confuses the brain and creates a central coherence. As a result, this creates distortions in the sense of one’s body and their environment, possibly leading to an out-of-body experience [6]. This same idea can be applied to how a faulty temporoparietal junction can cause an
out-of-body experience. If the temporoparietal junction is faulty, possibly caused by brain trauma, sensory deprivation, or other brain-related incidents, the temporoparietal junction could possibly interpret the vestibular signals incorrectly. This would once again cause confusion in the brain and cause it to lead to an out-of-body experience.

Yet, these experiences can also occur to a perfectly healthy person with none of those causes stated previously. The brain does such a great job of making humans feel like they are pinned to reality, but those pins are only part of an illusion. Instead, these pins can be shaken loose, and, sometimes, people will lose their sense of reality and experience an out-of-body experience [1].

Prognosis

Out-of-body experiences are not painful nor life-threatening. However, they have the capability to cause emotional distress due to the confusing and possibly frightening experience. If a healthy individual does not have any brain-related injuries or injuries to the inner ear and has experienced an out-of-body experience at least once, the likelihood of them experiencing it again is extremely unlikely. Even for those healthy individuals who may have not experienced it at least once in their lifetime, there is still mostly a 90% chance that they will never experience this event. It is mostly a rare event for healthy individuals. However, if an individual has any brain-related injuries or injuries to the inner ear, the likelihood of them having an out-of-body experience is much more likely than a healthy individual due to there being higher chances of malfunctions in either the temporoparietal junction or the vestibular system. The chances of these experiences occurring could be lowered by limiting any medications or drugs that can potentially alter functions in the brain temporarily. Regardless, those with those types of injuries, oftentimes, will experience these out-of-body experiences spontaneously many times in their lifetime.

Conclusion

While certain individuals have claimed that out-of-body experiences are related to mystical and spiritual means, there is no scientific evidence to prove this. On the other hand, there is scientific evidence that these out-of-body experiences are simply illusions caused by a misunderstanding between the temporoparietal junction of the brain and the inner ear of the vestibular system.

References


Trust Your Gut: How the Gut Microbiome Affects Brain Function

Aayushi Gandhi

Abstract
The human gut microbiome, which consists of trillions of microorganisms in the gastrointestinal tract, plays a key role in normal bodily functions [1]. Disruption of the gut microbiome can affect neural pathways in the body through the gut-brain axis [3]. Animal studies involving germ-free mice support the idea that disrupted gut microbiota compositions are associated with nervous system disorders due to the microbiome’s role in influencing immunity and producing chemical signals in the body [1]. Research indicates that dysregulation of the human gut microbiome is associated with Parkinson’s disease, autism, multiple sclerosis, depression, metabolic disorders, and other neurological disruptions [3]. The future of neuroscience research will rely heavily on regulating and manipulating the human gut microbiome to prevent and treat a variety of diseases and disorders [1].

Background
The human gut microbiome is the collective genome of microbes found in the gastrointestinal tracts of humans [1][2]. At approximately the same weight as the human brain, the human gut microbiome consists of trillions of nonpathogenic microorganisms that colonize the individual at birth and contribute to digestive, immune, and metabolic functions [3]. Initial colonization is influenced by several biological factors, including diet, hygiene, mode of delivery, and gestational age. Leading up to adolescence, microbial diversity of bacteria, archaea, viruses, and fungi increases drastically due to childhood exposures, such as feeding and playing. Consequently, the region tends to remain relatively stable for the rest of the individual’s life [1]. The gut microbiota is known for the crucial roles it plays in the progression of diseases as well as the protection they provide against lethal pathogens [2][3]. These microbes contribute to maintaining intestinal
homeostasis, breaking down food, and modulating Central Nervous System (CNS) development through circulatory, immune, and neural pathways [2]. The microbiota also frequently influences the development of autoimmune disorders, gastric disorders, and neurological conditions [3]. The Human Microbiome Project is an initiative launched by the National Institutes of Health (NIH) working to use developing technology to further study the human gut microbiome and its influence on medical conditions [7]. The project aims to understand the effects of the biosphere on human evolution and how medical and environmental biology interact to change the gut microbiome [8].

The Gut Microbiota-Brain Axis

The Gut Microbiota-Brain Axis is the method of communication used to pass signals between the Central Nervous System (CNS) and the gut microbiome [3]. The microbiome and immune pathways make up the gut-brain axis [10], The Enteric Nervous System (ENS) and the Sympathetic and Parasympathetic, which are subdivisions of the Autonomic Nervous System, are responsible for communicating with the gut-brain axis [2]. The CNS uses the axis to alter conditions in the gut microbiome through endocrine and stress responses. In return, the microbiome regulates homeostasis in the brain through neural, circulatory, and immune pathways [3]. These bidirectional interactions allow complex communication between the gut and the brain to regulate body conditions. If either end of the axis is disrupted, it can result in neurological issues [2].

Animal Studies

Many studies using animals have investigated the connection between the gut microbiome and the brain. The Maternally Separated Rat Model has been used to demonstrate the role of microbes in stress-related disorders [11]. In this model, dysbiosis, or microbial imbalance, of fecal microbiota significantly increases in the maternally separated mice compared to the control group. Factors, such as heat stress and crowding, in addition to maternal separation, affect the composition of their microbiota and thus enhance their systemic immune responses [11]. Treatment using Lactobacillus plantarum, a type of beneficial bacteria, on mice that were exposed to stress at a young age not only rectify depression-like behaviors, but also regulate immune responses and neurotransmitters in the treated individuals [12]. Neurotransmitter regulation is a method used to communicate with the gut-brain axis. Bacteria are capable of both secreting and consuming a variety of neurotransmitters, including dopamine, serotonin, and gamma-aminobutyric acid [13].

So far, rodent studies have also suggested that changes in the gut microbiomes of mice have notable impacts on their behaviors, including changes in their learning and memory capabilities as well as their personalities [14][15][16][17][18]. In 2011, a study revealed that mice initially identified as shy began to act more boldly when hosting microorganisms previously from the guts of more
intrepid mice [18][19]. In the same year, a neuroscientist and an immunologist at the Karolinska Institute in Stockholm communicated similar findings: germ-free mice were less apprehensive than mice colonized with the microbes of others. The pair’s research revealed that the striatum region of the brain in germ-free mice had higher turnovers of critical neurochemicals, such as serotonin [16][19]. Serotonin is a neurotransmitter that regulates behavior through interactions with other parts of the body that influence circadian rhythm and walking, which, in high levels, can induce inhibitory behavior [20][21]. Other studies revealed that germ-free mice have defects in their peripheral immune systems, thus emphasizing the overall importance of the gut microbiome to an individual’s immunity [1]. The immune system has a profound impact on brain functions because many nervous system disorders heavily rely on immune cells to change damaged tissue [22]. Scientists also observed that the germ-free mice had apparent shortcomings in the development of their musculature and epithelium, which are crucial in influencing the development of their guts [1].

Effects of Gut Microbiome Disruption and Dysregulation

Studies conducted with germ-free animals in past years have provided evidence that bacterial colonization of an organism’s gut is a crucial aspect in the development of their enteric and central nervous systems. The presence of microbes is commonly associated with the turnover of neurochemicals in the nervous system, since they play an important role in gut sensory-motor functions, such as gastric emptying (how long it takes for food to enter the small intestine) and distal propagation of migrating motor complexes (contractions that sweep digested food out of the stomach). The composition of the microbiota influences stress reactivity and anxiety-like behaviors in animals. Studies also indicate that germ-free animals have decreased levels of anxiety but increased stress responses and elevated levels of adrenocorticotropic hormone (ACTH) and cortisol. Researchers also report memory dysfunction in many of the germ-free animals, which is likely due to the modified expression of the brain-derived neurotrophic factor (BDNF) molecule [23][24][25][26][27][28][29][30][31][32]. Chemical signals initiated by the bacteria found in the gut microbiomes of humans can alter the lining of the gut to change the accessibility of signals being sent to the brain to influence brain functions [2]. The brain influences intestinal activities and functions of the gut microbiome through enteric neurons and immune, smooth muscle, epithelial, and enterochromaffin cells, all of which are also affected by activities of the gut microbiota [23]. Microorganisms from the gut microbiome can synthesize important neurotransmitters that act across the mucosal layer of the gut to influence the CNS and its ongoing development. Microbiota often secretes mediators that use the vagus nerve to influence centrally controlled functions of the body, such as behavior and stress responses [2].

Parkinson’s Disease (PD) is a nervous system disorder characterized by the degeneration of dopaminergic neurons. Patients with this disorder often experience tremors, slow voluntary movement, and rigidity [33]. Almost 80% of PD patients report gastrointestinal symptoms, such as constipation, dysphasia, drooling, and delayed gastric emptying, which corroborates the hypothesis that alterations in the human gut microbiome are risk factors for neurological disorders, such as PD [14][34][35]. Patient reports indicate that constipation, a symptom that has been associated with a lack of diversity in the gut microbiome in the past, is by far the most common gastrointestinal
problem [14][36][37]. Under the assumption that the composition of the gut microbiome can be altered, fecal transplants were used to successfully treat constipation in PD patients [14][38]. Epidemiological studies have also shown that there is a distinct difference in the microbiomes of PD patients versus controls [14][39][40]. In these studies, scientists observed that metabolic products of the human gut, such as short-chain fatty acids (SCFAs), were found in lower numbers in the guts of PD patients in conjunction with an overall lower level of microbial diversity [14][39][40][41].

Furthermore, there is evidence to support the claim that autism is impacted by gut microbiota as well. Autism is a neurodevelopmental disorder known to cause obstacles in social interaction in individuals who also experience anxiety, intellectual impairment, and seizures [2][42]. Children with autism were found to have more Clostridium, Bacteroidetes, and Lactobacillus species in their gut microbiomes, while the neurotypical control group had more Firmicutes species [1][4][5][6]. Autism has also been linked to lower levels of short-chain fatty acids, which are thought to be due to the lack of the necessary bacteria to properly ferment carbohydrates in the gut. Neuroscientists have also discovered that there is an association between the virulence, or severity, of autism and the gastrointestinal symptoms experienced by the patient; however, it’s possible that this correlation only exists due to the different eating habits typically seen in autistic children [1].

Additionally, the gut microbiome plays an important role in Alzheimer’s Disease, a common neurodegenerative disease in the elderly population, by influencing the patient’s cognitive behavior via the gut-brain axis. The risk of contracting this disease is affected by probiotic intervention and an individual’s diet because they alter the physiology of the gut microbiome. Neurodegeneration increases when the intestines and the blood-brain barrier become more permeable. Studies have shown that Alzheimer’s-related cognitive impairment correlates with imbalances in the gut and the microbiota population [43]. Additionally, Multiple Sclerosis (MS) is an inflammatory, demyelinating disease of the nervous system affected by a variety of genetic and environmental factors. Recently, scientists noticed that a notable percentage of MS patients experience constipation and gut permeability in addition to inflammatory bowel disease (IBD). The Human Microbiome Project has already shown that IBD is associated with the gut microbiome. A study examining the guts of MS patients found that they had more Pseudomonas, Mycoplana, Haemophilus, Blautia, and Dorea genera, whereas controls had more Parabacteroides, Adlercreutzia and Prevotella genera. These findings were consistent with the hypothesis that gut microbial dysbiosis is more prominent in MS patients [44].

In individuals with depression, researchers observed elevated cortisol levels and overuse of the hypothalamic-pituitary-adrenal (HPA) axis. An overexerted HPA axis can return to its normal state through colonization of the gut by Bifidobacterium infantis during adulthood [2]. Studies have shown that the microbiome impacts neurobiological features of depression, including immune activation and altered tryptophan metabolism [45][46][47]. With regard to gut barrier disruption, more and more evidence suggests that the gut microbiota is responsible for inflammation that characterizes metabolic disorders, such as type 2 diabetes, in addition to the aforementioned neurological disorders. Modifications of the microbial environment due to stressors can cause alterations in immune system activation, motility, and the gut barrier [2][48]. Researchers
discovered that enteroendocrine cells and the endocannabinoid system control gut permeability, which results in the release of microbial metabolites that play a role in such disorders [3][48].

The Future of Neuroscience and The Gut Microbiome

Recent research indicates that altering the human gut microbiome could be a treatment option for neurological disorders, such as Multiple Sclerosis, Schizophrenia, and Autism Spectrum Disorders (ASDs) [49]. Specifically for Multiple Sclerosis, researchers are looking to use microbial products to assist immune system regulation; however, for this approach to be considered, a comprehensive series of studies will need to be conducted to identify specific populations of microbes that are capable of secreting substances associated with the disorder’s potential treatment [1]. Furthermore, researchers have been creating germ-free mice that can provide the foundation for further gut microbiome experiments to study neurological effects. Human feces from donors, antibiotics, and antifungals will allow scientists to generate conditions that resemble the guts of humans in the gastrointestinal tracts of mice. Conclusions from mice studies with more humanized guts will hopefully provide more insight into how gut conditions affect diseases in humans [1].

In conclusion, research has highlighted that there is an important link between the human gut microbiome and the nervous system and has introduced crucial implications via the regulation of the gut microbiome. It is apparent that the gut microbiome will continue to play a key role in understanding neurological disorders and treatments well into the future [1].

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