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‘A Modern Biological Theory of Depression’
- Kevin Bao

‘Sleep - From Start to Finish: An Overview’
- Aditi Kona

INTERNATIONAL YOUTH NEUROSCIENCE ASSOCIATION
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Letter From the Editors
Sojas Wagle, Anita Singh, and Anushka Sarda

Dear Readers,

Welcome to the third 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:

Aditi Kona discusses sleep in a biological light, Maha Kirmani talks about the physical consequences of tackle football, Daisy Zhou examines free will experiments as well as an interesting syndrome called Capgras, Kevin Bao sheds light on an allele that is involved in depression, Lasya Kambampati evaluates the role of amyloid beta in Alzheimer’s Disease, Jasmin Alami delves into Tourette Syndrome, Parth Amin explores existing treatments for Parkinson’s Disease.

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
Anita Singh - Managing Editor
Anushka Sarda - Senior Editor
Aayush Setty - Senior Editor
Christine Zhou - Head of Assembly
Sleep - From Start to Finish: An Overview
Aditi Kona

Abstract
Sleep is a complex and dynamic process that is vital for the functioning of any human. On average, humans spend about one third of their lives sleeping, but the purpose of sleep remains largely unknown [1]. In recent years, research has brought to light many of the previously unknown mysteries of sleep. To this day, discoveries continue to be made as we try to uncover the details and inner workings of sleep. This article delves into the roles that varying structures play as well as the harmful consequences associated with the disruption of sleep. Furthermore, it discusses the factors linked with proper sleep and how one’s body responds through an average night.

Role of Genes and Neuro-transmitters in Sleep

Sleep is not a process controlled by a single structure or area of the brain. Instead, numerous parts work together in unison to achieve sleep. To start off, the hypothalamus, a peanut-sized structure deep inside the brain, contains groups of nerve cells that act as control centers affecting sleep and arousal. Within the hypothalamus is the suprachiasmatic nucleus (SCN) – a cluster of thousands of cells that receive information about light exposure directly from the eyes while controlling behavioral rhythm [2]. Damage to the SCN is linked with irregular sleep and is associated with feelings of sleepiness during the brightest times. This is due to the fact that the SCN is not able to match the circadian rhythm with the light-dark cycle. Although it might seem that this same disconnect would be apparent in blind people, studies have shown that blind people retain some ability to sense light and are able to modify their sleep/wake cycle accordingly [3].

Another significant structure to discuss is the brainstem which is located at the base of the brain. The brainstem includes separate parts called the pons, medulla, and midbrain, each with its own function. Through communication with the thalamus, the brainstem controls the passage between consciousness and sleep. Sleep-promoting cells within the hypothalamus and the brainstem produce an inhibitory neurotransmitter called GABA (gamma-aminobutyric acid), which acts to reduce the activity of arousal centers in the hypothalamus and the brain stem. The brain stem (especially the pons and medulla) also plays a special role in REM sleep. It sends signals to relax muscles essential for body posture and limb movements so that we don’t act out our dreams.
The thalamus behaves as a relayer for information from the senses to the cerebral cortex [4]. The distinction is that the thalamus stays silent during sleep, thus, allowing for peaceful rest without outside noise. In contrast, during REM sleep, the thalamus is actively sending the cortex pictures, smells, sounds, etc. to fill our dreams. There is much debate around whether the senses we experience through the day influence our dreams and continue to be an area of study. Regardless, the thalamus is responsible for providing the five senses associated with dreams.

Next, the pineal gland, wedged within the brain’s two hemispheres, receives signals from the SCN and produces melatonin, a sleep-inducing chemical. People who have lost their sight and cannot coordinate their natural wake-sleep cycle using natural light can stabilize their sleep patterns by taking small amounts of melatonin at the same time each day.

While mentioning the natural cycle of sleep, it is important to acknowledge the basal forebrain. This structure, part of the midbrain, works to promote sleep and wakefulness and acts as an arousal system. Release of adenosine (a chemical by-product of cellular energy consumption) from cells in the basal forebrain, and probably other regions as well, supports sleep drive [5]. Often, to keep themselves awake, people consume caffeine in the form of coffee or energy drinks. Caffeine counteracts sleepiness by blocking the actions of adenosine.

Lastly, we discuss the amygdala, an almond-shaped structure that becomes increasingly active during REM sleep. The amygdala is often known as the section mainly responsible for emotions and feelings; however, its specific function in REM sleep has yet to be discovered.

**Sleep Stages**

As it turns out, sleep is an essential neurological requirement for our bodies. There are multiple neurological structures intricately involved in the triggering and control of sleep periods. There are two basic stages of sleep: rapid eye movement (REM) sleep and non-REM sleep (which is further divided into three stages). Each stage is characterized by specific brain waves, neuronal activity, and patterns of breathing and heartbeats. A single cycle goes through all stages of non-REM and REM sleep several times during a typical night, with increasingly longer, deeper REM periods occurring towards morning [6].

To start off, Stage 1 non-REM sleep is the changeover from wakefulness to sleep. During this several minute period, the body experiences relatively light sleep as heartbeat, breathing, and eye movements slow, and muscles relax with occasional twitches. At this moment, brain waves begin to slow from their rapid steady daytime beat. Stage 2 non-REM sleep is once again a period of change as the body transitions and enters a
deep sleep. Both heartbeat and breathing slow, and muscles relax even further. Additionally, body temperature drops and eye movements stop. Since this is the longest stage, brain wave activity slows but is marked by brief bursts of electrical activity. Stage 3 non-REM sleep is arguably the most impactful stage as this is the period of deep sleep that allows one to feel reinvigorated in the morning. A person’s average heartbeat and breathing slow to their lowest levels during this period and muscles relax to the point where it is difficult to wake up. It is vital that the muscles are unclenched as it promotes an eased state of the body and allows for proper functioning. At this point, the body finally transforms into REM sleep which first occurs about 90 minutes after falling asleep [8].

REM derives its name from the vigorous side to side movement of the eyes behind closed eyelids [9]. The irregular frequency of brain wave activity resembles neuronal activity seen in wakefulness. Consequently, breathing becomes faster and irregular, and heart rate and blood pressure increase to near waking levels. However, the most notable characteristic of this stage is the vivid dreaming that occurs. Arm and leg muscles become temporarily paralyzed to stop one from acting out their dreams. Specifically, this is the stage that most people visualize when thinking of sleep; however, it continues to decrease in time as people age.

**Sleep Mechanisms**

One of the biggest questions is how the body regulates consciousness and sleep. How does it know when to transition into different stages of sleep or when to wake up? The answer to this lies in two key internal biological mechanisms: circadian rhythm and homeostasis. From body temperature and metabolism to the release of hormones, circadian rhythms control daily fluctuations. When someone naturally wakes up without an alarm, their circadian rhythm/biological clock is at work. Overall, it controls the general timings of sleep and consequently leads to sleepiness at night time. Circadian rhythms synchronize with environmental cues (light, temperature) about the actual time of day, but they continue even in the absence of cues. The actual need for sleep is kept track of by a process termed sleep-wake homeostasis. The longer someone is awake, the stronger the sleep drive gets. Thus, sleep is longer and deeper after a period of sleep deprivation. Factors that influence sleep-wake needs include medical conditions, medications, stress, sleep environment, and what someone digests [10]. Perhaps the greatest influence is the exposure to light. In fact, specialized cells in the retina take in light while simultaneously sending signals to either advance or delay the sleep-wake cycle.

Until about two decades back, sleep was just seen as resting that helped the body to recuperate. But the research studies about the brain and its functioning have led to some surprising ideas and conclusions about the biological necessity of sleep. So what and how does sleep help with the functioning of the brain? Specifically, what are the consequences associated with the disturbance of sleep?

**Sleep Disruptions**
Before we delve into the question above, it is vital to point out the damaging effects that a “clogged” brain can have. When the neurons in the brain are active during the day, they are consuming energy and produce by-products, like any living cell. Specifically, a toxic protein called beta-amyloid in brain tissue causes a variety of issues from slow functioning to deadly diseases. In fact, the accumulation of beta-amyloid is a characteristic common in Alzheimer’s patients. The body’s natural solution to this is sleep. Sleep activates a system that drains waste products from the brain. In turn, cerebrospinal fluid flows through the vessels surrounding blood vessels and removes beta-amyloid. This brain cleaning system was named glymphatic system as it was controlled by the shrinking and swelling of glial cells [11]. This indicates that the sleep activated cleaning system plays a role in the long term health and functioning of the brain.

Prolonged disruptions of sleep also have other health related impacts on the body, both short term and long term - leading to daytime fatigue, stress, type 2 diabetes and increased risk of high blood pressure and heart conditions [12]. Sleep disruptions can occur from environmental factors like noise and lack of suitable accommodations for sleeping, besides innate causes like sleep apnea.

References


Tackle Football: The Ultimate Concussion Generator

Maha Kirmani

Introduction

According to Bennet Omalu, “Over 90% of players who play to the professional level have some degree of [chronic encephalopathy].” [1]. Omalu was the discoverer of chronic encephalopathy (CTE), a disorder brought by multiple blows to the head. This concussion expert states that this degenerative brain disease is prevalent in NFL players and that a concussion is just the start for this disease to progress and grow. Tackle football is a sport that involves people getting tackled and severely injured, yet people support this game and continue to disregard all the science against such a sport. More awareness must be made about CTE so that measures can be put in place to help those who are affected by it and to prevent others from falling under the same affliction.

Background

Tackle football is a popular source of entertainment in the United States. Some say it’s the passion and love they have for the sport that causes them to play despite knowing all the dangers. Multiple studies suggest that the growing prevalence of chronic encephalopathy in NFL football players is causing serious damage to their lives.

High profile cases in recent years have brought to the attention of the public the risks of the sport and the damaging repercussions of CTE. While sports provide exercise and other benefits in general, it can’t be denied that the risks involved with football injuries are significant. Two players who’ve suffered from CTE include Aaron Hernandez and Bo Jackson. A minor incident of head trauma can become more damaging if treatment isn’t sought since the effects of the injury can encompass effects to brain chemistry that can alter one’s functions, moods, and memory entirely just as it did when Aaron Hernandez became a convicted murderer. He had a successful career in the sport, but it was discovered after the arrest and his suicide that CTE had a major influence on the actions he committed as his case was more severe than most for his age [2]. Even those who excelled in football, such as Heisman trophy winner Bo Jackson have admitted that the sport has become more violent and that with the increased awareness of CTE that he has now, would not have considered playing the sport if he knew of these risks at the beginning [3]. CTE does cause certain physiological disorders such as depression, memory issues, difficulty in the formulation of
tasks, and mood swings. Further effects include early manifestations of disorders such as Alzheimer’s and dementia.[4]. All of these on-sets of more consequences commences from the multiple concussions.

Scope of Impact

“A concussion is a traumatic injury to soft tissue, usually the brain, as a result of a violent blow, shaking, or spinning. A brain concussion can cause immediate but temporary impairment of brain functions, such as thinking, vision, equilibrium, and consciousness.” [4] This defines a concussion or mild traumatic brain injury. This is a common injury in many contact sports and is what directly causes increased chances of neurological disorders. One example can be found in the study of sports-related concussion in seven US high school and collegiate sports articles, which states, “A total of 375 concussions were observed. The average overall incidence rate was 26.1 per 100,000 athlete-exposures (95%CI: 23.5, 28.7; confidence limit ratio (CLR): 1.2), and the overall risk for an average season was 1.8 per 100 athletes (95%CI: 1.6, 2.0; CLR: 1.2). The incidence of concussion was highest in football, followed by women’s lacrosse, men’s lacrosse, men’s soccer, and women’s soccer.” [5] In this study, it was found that the sport with the highest rate of concussions was football. Out of all the other contact sports, football is shown with the highest rate of mild traumatic brain injury. In fact, nearly two-thirds of the incidents recorded in the study were from the football division. The rate of concussion was three times greater even in the practice in comparison to other sports. The nature of the sport contributed to these numbers since the investigators noted that tackling and getting tackled were both major contributors to concussions as it intensified more head to head contact. The issue isn’t addressed by the NFL and awareness of CTE is even more recent, but not enough is being done to resolve the issue.

Concussions, also referred to as mild traumatic brain injuries, can be the start of further neurological complications. After multiple concussions, there is a bridge that connects concussions to CTE. The bridge is known as post-concussion syndrome. According to the Sports Concussion Institute, “a history of developmental disorders, psychiatric disorders, or a history of headaches or migraines can play a part in concussion recovery time. Research suggests that for every concussion, the person is 1-2 times more likely for a second; 2-4 times more likely for a third; and 3-9 times more likely for a fourth.” [5] Headaches and mood swings are the most common symptoms of post-concussive syndrome and usually delay the recovery process which is dependent on the severity. This evidence also demonstrates that the more concussions a person suffers through, the higher the chance it is to get another one. The on-going and recurring concussions are what lead to brain degeneration

Current Repercussions

CTE, one of the many consequences of repetitive concussions, has been directly linked as a disorder very common in football players. Dr. McKee’s paper states, “recent reports have been published of neuro pathologically confirmed CTE in retired professional football players and other athletes who have a history of repetitive brain trauma. This trauma triggers progressive
degeneration of the brain tissue, including the build-up of an abnormal protein called tau. These changes in the brain can begin months, years, or even decades after the last brain trauma or end of active athletic involvement. The brain degeneration is associated with memory loss, confusion, impaired judgment, impulse control problems, aggression, depression, and, eventually, progressive dementia.” [6] Dr. McKee is a neuropathologist whose research has focused largely on CTE. Her paper suggests that CTE is a degenerative brain disorder that seems to progress over a long time. The impact of these successive industries alters the brain chemistry significantly even after the individual ceases any football activity. It seems to progress with consistent head trauma that occurs with many athletic activities such as American football.

The studies of concussions and one of its deadliest consequences primarily focus on one main sport: football. The rate of concussive incidents is highest in this sport and with these incidents come many devastating consequences. Concussions, or head trauma, in general, can all lead to CTE. Despite the increasing body of evidence that these injuries are directly linked to these undesirable outcomes, there have been no significant preventative measures taken yet. One measure considered to address the situation is instituting a total ban, but perhaps a better solution would be to reduce the rate of head to head contact during the sport. From concussions come post-concussion syndrome, this syndrome is the continuation of debilitating headaches long after the head trauma occurred. This syndrome progresses and becomes stronger after multiple head trauma occurrences, which eventually leads to CTE or other neurological disorders such as Alzheimer’s and dementia.

The underlying statement is football and CTE are inextricably linked. The strong association between brain injuries and CTE is the gateway to further cognitive impairment for these players, which will negatively impact the quality of life for themselves and those closest to them. The evidence implies that all concussions are unsafe, irrespective of their severity since they all have the potential to introduce further impairments.

References


The Neuroscientific Approaches to Free Will

Daisy Zhou

Abstract

As we all know, our behaviours and perception in this world are derived from the complex processing of our brains. However, to what extent does our brain control every decision we make? The question of free will has always been one of the most elusive questions for both neuroscientists and philosophers alikes and many experiments and theories have been extrapolated to explain this issue. In this essay, I will be mainly examining a few neuroscientific challenges to free will conducted by neuroscientists over time, evaluating their strengths and weaknesses, and ultimately examining new, favorable, and convincing ways of measuring free will.

Introduction

The definition of free will may vary, but the general concept of this philosophical property may be defined as the ability to act and make choices independent of any external influence[1]. More specifically, there are three categorical criteria of free will: the ability to do otherwise (the presence of more than one alternative), the control over one’s choices (being able to decide among options), and the responsiveness to reasons with rational motivation[2]. The most challenging view of free will is determinism, a philosophical idea that describes how there is a chain of cause in everything. This is now a dominating belief in neuroscience, especially as scientists are becoming more aware that there is a physicalistic foundation in everything and how the brain functions to carry out our behaviors and actions. However, it is worth noting that utilizing neuroscientific methods to explain the matter of free will must rely on the assumption of a direct connection between brain activities and decision making.

Libet’s Experiment

Benjamin Libet, a scientist in the 1980s, embarked on a journey of attempting to explain the nature of free will. He conducted an experiment in which he asked each participant to initiate a movement and report the moment that they had a conscious acknowledgement of their decision. By using electromyogram to record muscle the initiation of muscular contraction, and electroencephalogram (EEG) to measure Readiness potential (Bereitschaftspotential or RP) signals from the Supplementary Motor Area (SMA), which is involved in voluntary motor preparation,
Libet discovered that electrical signals of the brain initiated 350ms before the conscious awareness of decision making initiated. The firing of the neurotransmitter “dopamine”, which is involved in voluntary movements, seemed to initiate before the volitional intention to act as well. According to these results, it seems like the brain has already initiated signals to prepare for a movement before people become aware that they have made a free choice. The increased dopamine levels and firing rates support the previous EEG result, as the brain has already prepared neuronal transmission to initiate a movement to prepare for the conscious decision that participants are about to provoke. This experiment challenged the commonsensical view that people can make free decisions because these time lapses preceding volition could either allow or block the volitional process to achieve one’s volition, or to withhold the motor act [3].

Criticisms to Libet’s Experiment

However, criticisms of this experiment followed. Firstly, it is essential to have the correct understanding of the meaning of RP and what it encodes for because factors such as motor preparation, the anticipation of the initiation of movement, and the decision of when to move could all potentially be reflected in the RP. Also, measuring single-neuron firing rate may reflect temporal processing during the execution of a behavioral action rather than the pre-movement

![Graph showing RP, Intention to act, Action, and Performance](image-url)
preparation [3]. Moreover, Libet assumed that once the RP ramped up, an action would be inevitably initiated. Recently, studies have challenged this interpretation, as they have shown that actions can still be aborted after the RP has initiated, as robust RP may occur even in the absence of any perceivable movements, so there might be a certain degree of free will present. Subsequent tests on free will have followed. For instance, lateralized readiness potential (LRP) has established a modified version of Libet’s initial experiment that suggests a more accurate reflection of motor activity preparation, as a study by Jeff Miller and Judy Trevena suggested that RP is merely a sign of the brain paying attention[4] as pre-supplementary motor area activity is modulated by attention. In this experiment, the researchers found the same RP for both participants who initiated and didn’t initiate an action, which suggested that it doesn’t have a causal link with decision making. These results all suggest that RP encodes for processes rather than motor-action preparation, which questions the validity of the interpretation of free will using this experiment.

Kuhn’s and Marcel’s experiment

Other experiments were established to further tackle this problem. One of these was conducted by Simone Kuhn and Marcel Brass in 2008. In the first stage of the experiment, participants were asked to respond to a go-signal (a visual stimulus) on a screen by pressing a ‘go’ button as quickly as possible, and their reaction times (RT) were collected. Then, a quarter of the go-signals were transformed into different signals indicating either a ‘stop’ or ‘decide’ signal after a time-varied delay, and they had to stop their action with seeing ‘stop’ and either choose to 'stop' or ‘go’ when they see ‘decide’ as quickly as possible. If a RT is too short, it is categorized as an impulsive response without the capability to decide, and if a RT is longer, it belongs to decided action. The results have shown that there was a discrepancy between when subjects thought they made a decision, and when they thought they acted impulsively based on the RT data. Therefore, subjects are unable to tell the difference between a voluntary decision to resume an ongoing action and an inability to stop an ongoing action[5], as they can not tell whether an action was impulsive or deliberate. However, the results also suggest that there were certain incidences when participants successfully decided their choice, which may oppose a denial of a total illusional free will.
The answer to free will remains an unanswered problem in the 21st century due to a lack of convincing evidence without dubious criticisms. Therefore, what scientists need to focus on now is developing and optimizing new research projects and discussions to tackle this question, because the crucial problem of free will has crucial implications in both social and ethical aspects of the society, and how it may function differently in the future depends on the nature of free will and, in turn, the moral responsibilities that people should hold.

References


A Modern Biological Theory of Depression

Kevin Bao

Abstract
Purely biological theories of major depressive disorder (MDD) have waned in favor of a holistic approach in modern psychology, encompassing social, psychological, and other factors. The biological theories of depression still employed in medicine require revising. Recent evidence shows that depression is not just a chemical disorder localized in the brain that can be treated with antidepressants that target neurotransmitters alone. Depression is a body-wide disorder, and an effective biological approach to treatment must be holistic. The monoamine hypothesis is worth revisiting in light of new research that connects disruptions of biological mechanisms throughout the body to chemical changes in the brain. Even with the decline of a solely biological perspective, it’s been well established that the monoamine neurotransmitters serotonin, dopamine, and norepinephrine have a strong link with depressive symptoms. These chemicals are the main regulators of the limbic system—the emotional control center of the brain—and low levels strongly correlate with depressive symptoms.

Modern Theories of Antidepressant Mechanisms

The biggest shortcoming of the monoamine hypothesis is that monoamine levels rise within hours of consuming antidepressants, but depressive symptoms are only relieved after weeks of medication. If depression was indeed caused by low monoamine neurotransmitter levels, why don’t symptoms relieve when levels are raised? At best, this suggests that the relationship between monoamine neurotransmitters and depressive symptoms is not as straightforward as initially proposed; at worst, the monoamine hypothesis may need to be reexamined for its validity.

Recent research has managed to salvage the monoamine hypothesis by proposing alternate, slower mechanisms of action that are consistent with the delay before relief. Serotonin receptors require two components to function properly: the receptor itself and a G protein that converts the receptor binding to the release of the primary messenger cAMP, which is responsible for bringing about an appropriate cellular response. It has been observed in depressives that an abnormally high number of G proteins clump in lipid rafts in the cell membrane, which impairs their function [1]. As
a result, serotonin receptors do not detect serotonin properly. Accordingly lower levels of cAMP have been observed inside depressives, which lead to cell dysfunction and possible depressive symptoms regardless of the levels of serotonin. The study showed that SSRIs and MAOIs accumulated in the rafts when compared with non-antidepressant controls, displacing G proteins to other areas of the cell membrane where they can better function. Increased cAMP levels have been observed after antidepressant treatment. This is a slow process that better aligns with the symptom relief time frame observed in depressives that take anti-depressants.

More empirical evidence shows that when serotonin reuptake transporters are inhibited, sometimes dopamine reuptake transporters (DATs) will absorb the serotonin. The serotonin could then be excreted simultaneously with dopamine from the same dopaminergic terminal. Dopamine receptors are slightly sensitive to serotonin, but they will trigger if enough serotonin builds up [2]. This process takes up an extended period of time, again much closer to the timeframe of observed symptom relief. This shows that serotonin levels alone are not responsible for MDD and opens up a field of potential research of novel dopamine approaches to depression.

As part of a negative feedback loop to maintain controlled levels of serotonin in the synaptic gap, presynaptic 5-HT1A autoreceptors send a message that inhibits the secretion of more serotonin from the presynaptic neuron. Unlike postsynaptic receptors, autoreceptors are located on the presynaptic neuron but are also stimulated when bound to serotonin. When there is excess serotonin in the synaptic gap, 5-HT1A autoreceptors are stimulated more which results in less serotonin being secreted into the synaptic gap. This creates a contradiction with the theory that antidepressants work only by increasing serotonin levels in the synaptic gap: wouldn’t the decreased secretion of serotonin revert the increased levels brought about by SSRIs? This contradiction may be resolved by the fact that autoreceptors become desensitized and downregulated when chronically overstimulated. 5-HT1A autoreceptor overstimulation may be a primary mechanism of action for antidepressants that increase synaptic serotonin. However, more recent research proves this approach to be much more complex. SSRI treatment actually resulted in greater anxiety for mice that lacked the 5-HT1A gene [3]. However, increased metabolism of serotonin was also observed, which likely reverted the effects of increased secretion of serotonin due to the absence of 5-HT1A. Since 5-HT1A autoreceptor stimulation initially decreases synaptic serotonin before desensitization, this mechanism accounts for the delay before symptom relief. 5-HT1A autoreceptor agonists may hold potential as antidepressants. Full agonism of presynaptic 5-HT1A (as well as partial agonism of postsynaptic 5-HT1A) likely explains the antidepressant effect of buspirone, an anti-anxiety drug.

Tryptophan, a Precursor to Serotonin

Serotonin is synthesized from the amino acid L-tryptophan (TRP), but their relationship is more complex than direct. TRP must first cross into the brain through the blood-brain barrier before it can potentially have any effects on depressive symptoms after being converted to serotonin. When crossing the barrier, it must compete with other amino acids in passing through; the more competing amino acids (CAA), the less likely TRP will enter the brain [4]. Thus, the ratio of TRP to CAA is a measure of the potential for TRP to enter the brain, and the higher the ratio the
higher the potential for symptom relief. The obvious way to do this would be to increase serotonin levels, and indeed depressives are consistently observed to have lower TRP levels [5], and TRP supplements have been shown to reliably relieve depressive symptoms [6]. The second method of increasing TRP/CAA ratio is by decreasing CAA levels. One study has even suggested that a CAA abundance rather than a TRP deficiency is more responsible for depressive symptoms [7]. Injecting rabbits with insulin significantly decreases quantities of CAA, but also halved the amount of free TRP due to increased TRP binding to the carrier protein albumin in the presence of insulin [8]. Overall, the decreased CAA levels compensated for the decreased free TRP levels, and there was a net increase in the influx of TRP into the brain, which supports the findings of [7]. However, without further research into human subjects no firm conclusion can be made about insulin’s potential to treat MDD. There is little current research into CAA levels on depressive symptoms, but it holds great potential as a treatment approach.

Relief of symptoms after increasing the TRP/CAA ratio shows that there is still validity in a serotonin hypothesis. However, in order for this course of treatment to be efficacious, patients must already have an abnormally low TRP/CAA ratio; the higher the TRP/CAA ratio of a depressive, the less likely the increase of the ratio will result in symptom relief [9].

Early wakening and disruption of sleep/wake cycles is a common depressive symptom. Conveniently, one precursor of melatonin – the main hormone that regulates sleep/wake cycles – is serotonin. Also convenient is that melatonin levels fall when waking from sleep. It’s easy then to make the connection and theorize that since serotonin levels are lowered in depressives, melatonin levels may be lowered as well, possibly causing their levels in the brain to drop sooner when sleeping and cause early awakening. Low serotonin, possibly explains yet another depressive symptom, but chemical interactions are extremely complex and may not be this straightforward. Moreover, sleep stages in depressives are disordered, which further suggests disrupted melatonin levels, possibly due to disrupted serotonin levels.

The Inflammation Hypothesis and Tryptophan Metabolism

It has been observed that inflammation due to increased pro-inflammatory cytokine levels and increased release of glucocorticoids caused by a dysfunction of the immune system and hyperactive HPA axis accompanies MDD [10]. The inflammation hypothesis proposes that inflammation and MDD might be causally linked and that inhibiting the activity of cytokines may be able to combat depressive symptoms. The release of glucocorticoids from the adrenal glands is controlled by tropic hormones released by the pituitary gland and regulated by negative feedback. Glucocorticoids bind to glucocorticoid receptors (GRs) that inhibit the transcription of corticotropin-releasing hormone in the hippocampus, which mediates the release of ACTH, which stimulates the release of corticosteroids from the adrenal glands. In depressives, GRs have decreased function—possibly due to hippocampal damage due to excessive glucocorticoid release [11]—which results in failure of negative feedback regulation and further excessive release of glucocorticoids. This evidence provides a biological basis for the “downward spiral” of symptoms often reported by depressed individuals. Monoamine reuptake inhibitors have been observed to
increase GR mRNA, possibly restoring functional negative feedback inhibition of glucocorticoid release of the HPA axis [12].

The inflammation theory also provides some insight into the possible external causes for depression, since stressors can trigger a stress response from the HPA axis and prompt the release of both pro-inflammatory cytokines and glucocorticoids. This is one of the bridges between the biological and psychological approaches to treatment: Modifying biology by eliminating stressors through therapy instead of medication may be more effective for some individuals.

Increased glucocorticoid indirectly leads to less serotonin through its interaction with the second major TRP metabolic pathway, the kynurenine pathway (KP). Unlike the serotonin pathway, the KP disposes of excess TRP to help maintain homeostasis by converting it into kynurenine, which is then further decomposed into many catabolites. The first enzyme in the pathway, tryptophan 2,3-dioxygenase, limits the rate of pathway completion and is induced by glucocorticoids. Therefore increased glucocorticoid levels would increase TRP depletion through the KP and reduce TRP availability for serotonin synthesis, potentially leading to depressive symptoms. Empirical evidence supports this: treating patients with the synthetic glucocorticoid dexamethasone significantly decreases plasma TRP levels and TRP/CAA ratios [13]. Inhibition of the KP to reduce inflammation may be a potential treatment, though little research has been done so far.

The goal of the inflammation theory approach is to use anti-inflammatory medication to counter the effects of pro-inflammatory cytokines to alleviate depressive symptoms, and this form of treatment has been efficacious [14]. Nonsteroidal anti-inflammatory drugs have been the most successful at MDD treatment, likely because they do not lead to TRP depletion like glucocorticoids, which are steroid hormones that also act as anti-inflammatory agents.

This suggests that glucocorticoids are naturally released to counter cytokine-caused inflammation and that the use of anti-inflammatory drugs reduces the need for glucocorticoids, thus reducing TRP depletion. Though it is well-known that glucocorticoids act as the body’s anti-inflammatory agents, recent evidence suggests that chronic exposure to glucocorticoids may actually increase inflammation [15].

A meta-analysis shows that depressives have lower levels of kynurenic acid compared to non-depressives and antidepressant-free depressives have higher levels of quinolinic acid [17]. This makes sense considering that quinolinic acid is a glutamate agonist, and excessive stimulation of glutamate receptors causes excitotoxicity, or damage of neurons due to neurotransmitter excess in the synaptic gap. Ketamine, a channel blocker of the major glutamate receptor NMDA, is a major subject of current research and holds massive promise as an antidepressant. Alongside stimulating mTORC1 protein signaling with NV-5138, ketamine treatment acts extremely rapidly compared to current antidepressants, providing symptom relief within hours that lasts for about a week [18].
Neural damage caused by quinolinic acid likely correlates with depression and is worth investigating in future studies.

Treatment with antidepressants—including serotonin reuptake inhibitors—results in an increase in kynurenic acid levels. This suggests that depressives have a dysfunctional KP that’s shifted towards the end of the pathway and the production of quinolinic acid. Antidepressants have yet another potential mechanism of action: restoring normal function of the pathway by shifting it towards the beginning of the pathway by increasing production of kynurenic acid.

**Epigenetic Influence of Glucocorticoids on the Onset of MDD**

The serotonin transporter (5-HTT) is a protein that facilitates reuptake of serotonin, and it has been discovered that polymorphisms exist for the protein’s gene, SLC6A4: a short (s) and long (l) allele. The gene itself does not directly cause depression, but rather it influences the likelihood of the development of depression following stressful life events. This further provides evidence for a relationship between stress-related glucocorticoids & inflammation and depression. Individuals with the (s) allele are more likely to develop depressive symptoms than individuals with the (l) allele. Homozygous (s) genotypes are the most likely to develop symptoms, followed by the heterozygous and homozygous (l) genotype [19].

The theory behind that is (s) allele leads to less production of functional transport proteins, leading to dysregulation of serotonin reuptake and less control over serotonin levels in the synaptic gap. Accordingly, individuals with the (s) allele have lower levels of 5-HTT mRNA.

Also, it has been observed that increasing dexamethasone doses results in increased serotonin reuptake across all genotypes [20].

A systematic review of 67 studies reveals that increased DNA methylation of SLC6A4 and BDNF in general is heavily associated with MDD [21]. BDNF is involved in neurogenesis and neuron maintenance, and decreased BDNF levels along with excitotoxicity may explain the decreased neuron branching observed in depressives, which further demonstrate the massive potential of ketamine—which leads to the creation of new branches — as an antidepressant. Studies inside the review were also able to pinpoint specific CpG sites that were heavily associated with MDD, and there were also contradictory findings for the association of MDD with methylation of other genes, including NR3C1 and OXTR. The SLC6A4 (s) allele is associated with lower levels of mRNA, which is associated with methylation. Also, females also have higher CpG methylation and lower mRNA levels of the 5-HTT gene, providing a molecular explanation for the higher likelihood of females to develop depression than males [22].

Treatment with serotonin and norepinephrine reuptake inhibitors tended to decrease 5-HTT mRNA, and tricyclic antidepressants increase GR mRNA [23]. Also, Caucasians
homozygous for the (l) SLC6A4 allele tended to respond better to SSRIs [24]. Both of these suggest that interactions with genetic material may be another antidepressant mechanism.

**Conclusion**

The monoamine hypothesis is not as outdated as some may argue it to be. Although notions about the pharmacological mechanisms of antidepressants may need to be reevaluated, modern research has paved the way for promising new theories. However, the idea that monoamine reuptake inhibitors solely affect neurotransmitter levels in the synaptic gap must be discarded in light of overwhelming new evidence that suggests mechanisms independent of reuptake inhibition.

The strong link between biological disorder and MDD shows that there is value in focusing more on the biological approach to depression when it comes to research and diagnosis. It may even suggest that depression is ultimately a biological disorder and that psychological disorder may merely be a symptom, especially considering the biochemical changes caused by stressors.

Research into the biology of depression is still in its infancy, and many more studies must be conducted before firm conclusions can be drawn. Medications that specifically target newly discovered depression mechanisms—instead of their targeting with conventional antidepressants only being a side effect—might bring about new classes of next-generation antidepressants. By understanding the underlying pathological causes of depression, the efficacy of newer medication can be increased by targeting a broader range of biological mechanisms.

Alongside the development of new treatments, a deep understanding of the biology of depression should help bring about a new, more accurate diagnosis criterion based on objective medical testing rather than just the psychological criterion currently outlined in the DSM-5, which is arguably arbitrary, subjective, and inaccurate.

**References**


Amyloid Beta in Alzheimer’s Disease

Lasya Kambampati

Abstract

Amyloid beta has long been recognized as the most prominent molecular feature of Alzheimer’s disease, along with tau tangles. In this paper, we will explore Alzheimer’s disease by studying amyloid beta. We will discuss the history of amyloid beta and its role in Alzheimer’s disease, as well as explore its properties, what makes it so toxic, and the evidence that verifies its role in Alzheimer’s disease. Furthermore, we will explore the relationship between Amyloid beta, Alzheimer’s, and the lipid membrane. Finally, we will discuss possible avenues of treatment and current areas of research.

What is Alzheimer’s Disease?

Alzheimer’s disease is a neurodegenerative disease in which brain cells that process, store and retrieve information degenerate and die. It causes progressive memory impairment and loss of cognitive function. Symptoms include mental confusion, forgetfulness, loss of basic cognitive abilities, and on a more molecular level, aggregates of amyloid beta protein plaques and tau tangles on blood vessels and neurons [1]. Scientists believe that oligomers cause amyloid toxicity and are working on preventing aggregation of amyloid beta. An oligomer is a chain of a few repeating units. Researchers are also creating more accurate models to study the molecular changes that amyloid beta and potential treatments cause. As of right now, there is no cure or prevention for Alzheimer’s disease.

What is Amyloid Beta?

Amyloid beta oligomers are the most prominent aspect in the molecular pathology of Alzheimer’s. An amyloid beta oligomer is part of a larger protein, known as amyloid precursor protein, that extends from the inside of brain cells to the external environment [2]. Later, it is cut into separate pieces when activated and, in some situations, a beta-amyloid is produced.
In Alzheimer’s, amyloid beta gathers around synapses, disrupting communication between neurons, leading to their death. The oligomers are more toxic if they are small and soluble[2]. The amyloid hypothesis assumes that problems in production, accumulation, or disposal of this protein lead to the symptoms. The mechanism behind the toxicity of these oligomers is believed to be destabilization of homeostasis through the formation of new ion channels in lipid bilayers. Scientists still don’t know the exact mechanism behind these changes which could help develop new treatments.

What is the evidence for amyloid beta relation to Alzheimer’s?

Scientists have been able to prove that amyloid beta is directly linked to Alzheimer’s. Looking at families across the globe, scientists have been able to pinpoint specific genes that nearly always guarantee development of Alzheimer’s disease. One example is the APP gene which codes for amyloid beta. These mutations are all associated with amyloid beta production. Furthermore, in experiments with genetically engineered mice, scientists found that mutations in only the amyloid beta gene lead to Alzheimer’s symptoms. In addition, those with Down syndrome, who have three copies of the APP gene, almost invariably develop Alzheimer’s disease.

The Dynamics of Plaque Formation

One of the biggest reasons that amyloid beta causes so many problems is that it is chemically “stickier” than other fragments produced when APP is broken. The protein clumps into clusters known as oligomers. As the disease progresses, the oligomers link together, becoming fibrils. Fibrils join together to form beta-sheets, which can join together to form plaques[2]. The plaques are most prominently seen in pictures and contain clumps of various systems.

What is the Relation Between Amyloid beta, Alzheimer’s and Lipid Membranes?

Not only does beta-amyloid play a significant role in Alzheimer’s disease, changes in the lipid membrane also play a part. There are changes in the phospholipid bilayer to sphingomyelin and gangliosides. Sphingomyelin has been consistently shown to decrease in Alzheimer’s disease [3]. Gangliosides, however, has conflicting results. Some studies show that it increases and others say it decreases; similarly, studies are conflicted on whether or not it
decreases or increases the probability of plaques and tangles forming [4][5]. Although some lipids have produced conflicting results, on the whole researchers have found the lipid concentrations and Alzheimer’s (specifically damage to neuronal membranes) are linked and can be used as an indicator [5].

These changes in lipid composition of neuronal membranes affect properties such as membrane fluidity, permeability, and domains. These all affect the way amyloid binds in the brain and, therefore, the course of Alzheimer’s disease. At the time, there are no models in the literature that can accurately model healthy and AD membranes. In order to study the changes that happen to the lipid membranes and their effects on AD, scientists have, in the past, used a simple lipid model [6]. Oftentimes the results from such studies can not be directly related to the human body or actual animal subjects as they don’t represent the cell accurately enough. Scientists have begun to pick aspects of the membrane and feature them prominently in the model in order to create a more representative model. Some areas of focus are the DPPC, POPC, sphingomyelin, cholesterol, and ganglioside GM1. [7] In this way, the resulting experiment’s results could be used to mimic healthy and diseased states of real neurons.

To explore the specific changes in the neuronal model with the new model, researcher Elizabeth Drolle designed an experiment. There were three experimental groups: normal, decreased GM1 (ganglioside), decreased GM1 and SM (sphingomyelin)[7]. These specific lipid changes were picked because they were observed in vivo most often. Drolle measured the morphology and electrical surface potential of the neurons using BLM (Black Lipid Membrane), POPC (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine) and AFM (a type of imaging to view topography of a model). The results showed that the changes in lipid membrane content changed the membrane permeability - throwing the neuron out of homeostasis[7]. Since ion concentration is essential neuronal signaling, these membrane changes caused damage to normal cell function. Particularly in AD cells, these changes also allow amyloid beta to penetrate further into the cell, further increasing its toxicity. This discovery opens up a new avenue for treatment research.

In addition to these changes, Drolle’s results lead her to a new hypothesis regarding amyloid’s toxicity. This theory postulates that amyloid has protective roles in the brain to fight against the bacteria and microbes without affecting the host cell. AMP’s (antimicrobial peptides) such as amyloids are able to recognize bacterial membranes using electrostatic interactions[7]. These changes in the neuronal membranes prevent amyloid beta from performing its normal function and cause amyloid beta plaques to build up. If we were able to prevent this, we could prevent mass cell death.
What are potential avenues of treatment?

Scientists have been looking for a treatment for Alzheimer’s disease for decades. However, until the drug known as aducanumab, there was no large-scale successful therapy discovered. It was the first drug that was shown to have a positive effect in studies on Alzheimer’s disease by binding to amyloid beta and reducing the rate of cognitive decline. The drug is currently in clinical trials but it opened up new avenues for scientists to study treatments. Some directions are outlined below:

Decreasing Production:

Current research aims to change the behavior of the enzymes and proteins that break amyloid precursor proteins into smaller fragments. These proteins are known as secretases, with beta and gamma secretases being the most prominent [9]. Scientists are either trying to change the interactions the enzymes have with APP (i.e. to create fragments other than APP) or create drugs that block the secretases.

Preventing Aggregation:

Scientists are also exploring drugs that can prevent the formation of the fibrils, mats, and plaques discussed above as some studies indicate that the toxic effects of beta-amyloid begin before the separate molecules begin to interact. Some methods include “mobilizing the immune system to produce antibodies to attack beta-amyloid, administering laboratory-produced antibodies to beta-amyloid and administering natural agents with anti-amyloid effects”[9].

Antibodies:

There are two types of antibodies being studied: active and passive vaccines. Active vaccines have a virus or protein that has amyloid beta attached. Theoretically, this should prompt the body to produce antibodies in response and reduce levels of amyloid beta in the brain. Passive vaccines, on the other hand, are predetermined doses of antibodies that can be produced in the laboratory. In this way, the vaccine doesn’t rely on the body to produce antibodies but directly supplies them. In addition, some researchers are looking into natural agents with anti-amyloid properties such as IVIG, intravenous immunoglobulin in the plasma of human donors [9]. It has been shown to contain natural antibodies that could reduce amyloid beta levels.

References


A Strange Brain Disorder: Capgras Syndrome

Daisy Zhou

Abstract

As one of the strangest delusions that is not being widely recognized, Capgras Syndrome is a disorder in which patients believe their close friends or family members are imposters because they do not have any emotional attachment to them. The following essay is a general overview of Capgras Syndrome, given its symptoms, neurological causes, treatments, and precautions in caretaking. The first section summarized the ‘landmark’ symptoms of this psychiatric disorder, the second section outlined several possible pathological causes with relevant statistics, then possible treatments are identified, and at last precautions for the family members of CS patients are given. This article does not only provide an introduction to people with this psychiatric delusion, but also spreads awareness of this disorder and encourages more research to be done.

Introduction

Imagine a man who believes his wife is no longer his wife but her doppelgänger. While you may think this is a ridiculous joke, there are patients in the world who are struggling with this delusion every day — the Capgras Syndrome (figure 1).

Capgras Syndrome (CS), or Capgras Delusion, is the most common type of delusional misidentification syndromes (DMSs) that involves the everlasting denials of familiar people or objects as if they are replaced by imposters, and patients believe they can see through the “disguise” as they are aware of the replacement (figure 1). This delusion may result in violence and anger towards the “imposters,” anxiety and stress towards someone’s own life, or changes and effects in social behaviors. This disorder hardly ever exists in its pure form and it is
normally accompanied by other neurological or psychiatric conditions. One of the four conditions can occur in a CS patient: 1. the person is recognized, and the patient asserts the resemblance of the double to the misidentified significant other; 2. no identity is attributed to the double, who has neither name nor existence; 3. the double is an imposter, pretending to be the original they are replacing; 4. the original has disappeared, his/her absence remaining unquestioned [2]. One of the most intriguing phenomena in CS patients is that they recognize the close relation and the significant other’s face, but utterly deny the person’s identity [3].

The absence of consensual clinical criteria for Capgras Syndrome diagnosis renders the epidemiological data uncertain and makes the prevalence of CS more likely to be underrated [4]. Among 60% of CS patients suffer from schizophrenia spectrum disorders and 20%- 40% of the patients also have other organic illnesses [5]. Also, family history of psychosis is reportedly present in half of CS patients [6].

Explanations for Capgras Syndrome

There are two components of the visual recognition of a familiar face: the conscious recognition of faces and the memory of their related semantic information, and limbic-mediated emotional arousal, or familiarity. As CS patients are able to recognize but not acknowledge familiar faces, the syndrome suggests that there are two separate circuits in the brain for facial recognition: a
cognitive circuit impaired in prosopagnosia, or face blindness, and an affective circuit which is impaired in CS. [8] In the affective circuit, the dorsal visual track that gives the face its emotional significance is damaged (figure 3).

The pathological reasons for the occurrence of the delusion are still unknown. However, various theories suggest possible neurological causes. One of the theories was proposed by Hirstein and Ramachandran in 1997 after they observed that CS was more frequently caused by lesions in the ventral (occipitotemporal) pathway that connects the amygdala [9]. Because the amygdala is an emotional center in the limbic system, the scientist extrapolated that there might be a disconnection between the amygdala and Fusiform Face Area (FFA), a region specialized for face recognition. As these regions disconnect, even if a person succeeds to recognize the face of a familiar person, the limbic system can no longer invoke the sense of familiarity, which in turn leads to the lack of emotional attachment of this person. Also, it has been suggested that CS results from the disconnection of the face processing regions in the inferior temporal lobe from structures in the limbic system, especially the amygdala, which is very important in assigning emotional value to familiar faces. [10] Another theory in the book Mapping the Brain suggests that there might be a disconnection between the limbic system and the frontal lobe. Because the frontal lobe is involved in the acknowledgment of the sense of familiarity that the person receives after his family members are processed in the limbic system, the signals cannot be delivered in the frontal lobe when it’s damaged, so the person does not ‘feel right’ even though he noticed that there are emotional linkage between the familiar person and himself. [11]

Also, other theories suggest Lewy body dementia (28% of the cases) or other neurodegenerative diseases like Alzheimer’s (15% cases of CS) can induce the delusion as they alter the patient’s perception about the world around them [12]. Besides, schizophrenia may induce various delusions, and epilepsy may trigger damage or hypersynchrony of neural activity so they are regarded to have potential relevance to CS [13]. Interestingly, more widespread bilateral frontal and temporal cortex atrophy in schizophrenia patients with CS than schizophrenia patients without the syndrome by using computerized tomography (CT). [14] Neuroanatomical
examinations of CS patients suggest a higher chance of structural and metabolic abnormalities in
the right frontal, temporal, or parietal brain regions.

Lastly, psychodynamic theories suggest that CS might be an anxiety-induced regression of
cognitive and emotional functioning, pathological splitting of internalized object representations,
insufficiently repressed conflicting or ambivalent feelings toward the implicated person, and the
projection of negative emotions that come to light from these conflicting feelings.

**Possible Treatments**

As the physiological causes of CS have not been exactly identified, the treatment of its
symptoms is still in the phase of ‘trial-and-error’. Many possible medications or medical procedures
can be taken to control the symptoms of CS:

- Pharmaceutical treatments related to dementia might be used to alleviate the
  symptoms. CS patients are sometimes responsive to typical and atypical
  antipsychotics such as olanzapine, risperidone, quetiapine, sulpiride, trifluoperazine,
  and pimozide [16].
- Pharmacological treatment of CS is based on antipsychotics, antidepressants,
  anticonvulsant, and benzodiazepines considering patient needs and characteristics.
- As studies have reported a overactivity of dopamine levels in CS patients[17],
  medications like cholinesterase inhibitors, a drug that boosts neurotransmitters by
  inhibiting the enzyme that breaks down acetylcholine, may be helpful to cognitive
  symptoms in patients, such as memory and judgment.
- Antipsychotics and therapy for schizophrenia patients or possible surgery for brain
  lesions if identified may have a positive impact on CS patients as well [18].
- Electroconvulsive therapy (ECT) has been reported to benefit either alone or in
  conjunction with antipsychotics, mood stabilizer, or antidepressant medication in
  patients with CS. [19]
- Cognitive behavioural therapy (CBT) may be a utilized form of psychotherapy
  intervention in some cases by assisting the patient to overcome the delusional beliefs.
  [20]

**Precautions to Family Members of CS patients**

As violence towards familiar people might be prevalent, especially violence induced by
male patients, families may consider carefully the frequency and the time of visit during the day,
and caretakers should continuously reassure patients that they are safe. Also, the family members
of the patients can announce the identity of themselves before being seen by the patients to gradually
establish trust and emotional connection with them. Another useful tip is to utilize auditory
interactions rather than visual ones as patients are highly sensitive to visual cues, which may in turn
trigger aggressive or anxious behaviors due to the delusion.
References


Tourette Syndrome – Life with Tics

Jasmin Alami

Abstract
The first recorded case of Tourette syndrome was in the year 1885. The French neurologist Georges Gilles de la Tourette described symptoms of involuntary, uncontrolled movements and sounds in nine of his patients [1][2]. Named after this doctor, today, the disorder is called Tourette syndrome and its main characteristic is tics, which are exactly what Gilles de la Tourette described many years ago. In addition to these tics, there are other disorders that often accompany Tourette’s. This article will discuss in detail what tics are, how the brain is altered in affected people and which methods are used in the treatment of this disorder.

Symptoms and Diagnosis

Tourette Syndrome (TS) is characterized by tics, which are involuntary, sudden, and repetitive vocalizations or movements [3]. They first appear during childhood, usually at the age of four to six, and are about four times more common among boys than girls [1][3]. They continue to become worse until their severity peaks in the early teen years. The symptoms of most TS patients then improve during adolescence and might even disappear completely [3]. As mentioned before, tics can be movements or vocalizations and they are categorized accordingly. First, there are motor tics. Most commonly present in the head and shoulder area, however they may later become more complex and spread to the extremities. Examples of common motor tics include blinking, twitching, and grimacing of the face [3]. The second type of tics, vocal tics, are sounds the patient produces with their voice, such as humming, clearing the throat or yelling certain words or phrases. Echolalia, repeating someone’s words, and coprolalia, yelling inappropriate words, account for other forms of vocal tics [4]. Another component of a tic, other than the actual execution, is the premonitory urge, which a patient experiences in the moments leading up to the tic. One could compare it to the moment

Figure 1. The different aspects of Tourette syndrome [8].
before sneezing when you can already anticipate the sneeze [3]. Completing the tic relieves this premonitory urge [5].

In addition to tics, people suffering from TS have a high chance of comorbidity with several other disorders with about 90% of the patients experiencing such. Especially common are attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). Another potential comorbid condition is autism spectrum disorder (ASD) [5].

Diagnosing TS is not as easy and definite as diagnosing many other disorders because no single test exists. This is why a clinical diagnosis is based on the expression of the symptoms. A person has Tourette’s syndrome if they express both motor and vocal tics over the course of at least one year [4].

**Pathology**

The cause of Tourette Syndrome can be attributed to genetic as well as environmental factors and is a very complex subject matter [5]. As to the genetic origin, there are many genes involved in the development of TS. And even though no single gene has been found responsible so far, the presence of a genetic connection is commonly accepted [6]. In many cases, a child with a parent that suffered or still suffers from Tourette syndrome is more likely to develop the disorder themselves [5]. Nevertheless, it was shown that genetic factors do not solely account for the cause of Tourette’s. Environmental factors such as heavy smoking during pregnancy and complications during childbirth can influence the development of the syndrome as well [6].

Regarding the pathophysiology of Tourette syndrome, several scientific studies suggest that the underlying changes are spread over many areas of the brain rather than concentrated in one place. For one, there is a reduced number of GABAergic interneurons, which would normally inhibit the cortico-basal ganglia pathways [5]. The basal ganglia play an important role in the production of motor movements. Thus, there is no proper inhibition of movements in TS patients. Additionally, neural circuits that connect the limbic and sensory systems to other structures are also affected by this disinhibition, which accounts for the sensory aspect of the syndrome. Finally, the neurotransmitters histamine and dopamine are implicated in the genesis of TS because they are present in abnormal levels [5].

**Treatment**

Although tics are involuntary, it is possible for some affected patients to temporarily suppress them. However, this suppression has exhausting effects and is not a long-term solution. Another way of ameliorating the symptoms is concentrating on a calm activity that includes fine movements. Focusing on playing an instrument or playing a sport, for example, can make the tics less severe. In contrast to that, stress can worsen them [3]. Still, these
methods are only temporary and have no long-term cure. As no such cure has been found yet, treatment is symptomatic [4]. Because many patients' lives are not drastically affected by the tics, it is not necessary to treat them in this case. If they do interfere with everyday life or are painful, medication can be used to treat Tourette syndrome [4]. Drugs used in treatment include alpha-adrenergic agonists, antipsychotics, botulinum neurotoxin, and sometimes cannabinoids [7]. It is important to note, however, that these drugs cannot be taken mindlessly as they carry a variety of side effects with them [1]. An alternative approach is behavioral therapy, where the patient learns to recognize the premonitory urge and replace the tic with another, more healthy habit [5]. If the tics continue in their severity and significantly disable the patient, deep brain stimulation is an option for adults. This is an invasive procedure that targets structures of the basal ganglia [7].

Conclusion

As much as we know about Tourette syndrome, there are still many secrets about it to be discovered. Research is currently being done in order to find out more about its cause and the effects on the brain, with the goal of finding better treatment options or even a cure in mind [5]. The future needs to focus not only on the biochemical aspects of the disorder, but in equal intensity on the behavioral and social causes and effects on an individual. Being different and mocked for it can take a big toll on a young child’s psyche and can – regardless of whether their tics improve – have a long-lasting impact on their life. It is therefore necessary for us as a society to not only progress the research on the topic, but also raise public awareness and acceptance of Tourette syndrome.

References


Parkinson’s Treatment: Where We Are and How We Got There
Parth Amin

Introduction
Parkinson’s disease is a very severe and life-threatening neurodegenerative disease that affects nearly one million people in the United States, who are aged usually 60 and above [1]. The basal ganglia, found in the center of the human brain, is an important subcortical region that is responsible for many innate and fixed motions and cognitive abilities: eye movements, involuntary locomotion, thought, and memory [2]. Parkinson’s originates from the degeneration of neurons in the substantia nigra, a region in the basal ganglia, seen in figure 1.1, that relies on the neurotransmitter dopamine for relaying signals [3]. The loss of dopamine results in many symptoms that may hallmark the effects of Parkinson’s, such as tremor, impaired posture, parkinsonian gait, and bradykinesia [3]. How far has medical research come to treat this seemingly common and serious disease? Is simply treating with dopamine enough?

Treatment
Until recently, Parkinson’s was untreatable and patients could only take medication to reduce the symptoms they were facing. However, in the last decade, we have seen promising results from two agents: Coenzyme Q10 and Rasagiline. Coenzyme Q10, unfortunately, has experienced mixed reviews. Coenzyme Q10, or CoQ10, is an antioxidant that plays a role in the mitochondria by uptaking dopamine for cellular use. CoQ10 was sought by researchers as a cure for Parkinson’s because the enzyme has a high affinity for retaining dopamine [4]. An annual research project conducted on over 650 patients found that there were miniscule differences between those who were treated with placebo and those who were treated with varying concentrations of CoQ10 [4]. Thus, research for CoQ10 has temporarily been halted.

Figure 1. Mandar Jog, CEO Magazine. Image compares a healthy basal ganglia to one that is affected by Parkinson’s [40].
Rasagiline, on the other hand, has been showing promising results. Rasagiline is a drug that falls under the category of monoamine oxidase (MAO) inhibitors. Other drugs, such as selegiline and tranylcypromine, are also considered to be MAO inhibitors. These drugs, however, are not approved by the FDA for treatment, hence the reason why Rasagiline is so sought after [5]. Rasagiline is important because it can impair the enzyme monoamine oxidase, seen in figure 1.2, from binding to active sites and breaking down important neurotransmitters such as dopamine, norepinephrine, and serotonin [6]. So far, Rasagiline is the only medication that not only lessens the symptoms of Parkinson’s, but also modifies the disease itself, providing neuroprotective benefits for future onsets[6].

How Far Has L-Dopa Treatment Came?

As mentioned earlier, no lab tests can be conducted to diagnose someone with Parkinson’s; instead, clinicians have to rely heavily on the patients’ medical history and symptoms. If the patient is experiencing some of the symptoms mentioned above, then a treatment known as Levopada, or L-Dopa, is prescribed. When first introduced in the 1960s, the treatment was met with a number of issues. The drug had to be taken in high levels to alleviate symptoms of motor dysfunction present in the disease. This caused severe nausea, causing patients to prefer the symptoms of Parkinson’s over those caused by L-Dopa.

L-Dopa has become the “Gold Standard” for Parkinson’s treatment today. The drug simply compensates for the lack of dopamine found in the substantia nigra, seen in figure 1.3, by preventing the reuptake of dopamine and increasing neural dopaminergic neurotransmission. Though one may question: Can one simply not reuptake dopamine through controlled dosages? To answer that, the blood brain barrier, which separates circulating blood from the brain, prevents dopamine from entering. L-Dopa, being the precursor of dopamine, can bypass this barrier and can be turned...
into dopamine by enzyme Dopa Decarboxylase when it reaches the depleted areas. However, Dopa Decarboxylase can also break down L-Dopa throughout other parts of the body. To make sure most of the L-Dopa stays intact for it to be broken down in the brain where it is needed, another drug called carbidopa is also taken with L-Dopa. Carbidopa blocks the enzyme Dopa Decarboxylase throughout the body, allowing for sufficient amounts of L-Dopa to reach the brain, where it is needed [7].

As research progressed, more proteins, such as catechol-o-methyltransferase (COMT), were found to disrupt L-Dopa function, breaking it down into dopamine before it reaches the brain. Discovered in the 1980s, drugs such as entacapone and tolcapone were developed to inhibit the protein COMT from acting, which allowed for L-Dopa to be more effective [8]. Entacapone and tolcapone, however, have become less popular as L-Dopa is less expensive and more convenient to uptake.

**Protein Buildup in Lewy Bodies**

Another phenomenon of Parkinson’s disease is the buildup of proteins in aggregates called lewy bodies. Lewy bodies are distinct features in nerve cells of people with dementia and Parkinsons. Thus, through using MRI and CT scans, clinicians can diagnose one with either Parkinsons or Lewy Body Dementia if he or she finds ample amounts of the aggregate in nerve cells.

A-Synuclein (SNCA) is the protein responsible for the formation of lewy bodies. Researchers at Osaka University’s Graduate School of Medicine, in efforts of finding a cure that can prevent the cause of Parkinson’s disease rather than its symptoms, developed a gene known as antisense oligonucleotide (ASO), through a process called amino-bridging. This gene blocks the translation of the A-Synuclein protein by up to 60% (seen in figure 1.4) [9]. Through mouse treatment, lead author Takura Uehara claims that ASO has significantly reduced the symptoms of Parkinson’s within only 27 days of administration. Through ASO, Uehara and his team hope to expand their work to possibly help cure Lewy Body Dementia, which, as mentioned earlier, is also caused by the accumulation of the A-Synuclein protein.

**The Future of Parkinson’s Treatment**

![Figure 1.4: Data from Osaka University’s study showing the marginal effects ASOs have on blocking SNCA translation [g].](image-url)
As Rasagiline and L-Dopa continue to make strides in neuroscience research, we must understand that there is no medication or treatment plan currently available to address and cure Parkinson’s. In fact, there is still more research being done on the disease itself. There are still neuroanatomical and molecular cues that are not researched well enough to understand the exact cause of Parkinson’s disease. Sure, there are genetic markers, physiological structures, and environmental factors that result in the loss of dopamine in the basal ganglia and the formation of proteins in lewy bodies, however, the question still remains: How can we mitigate such markers, structures, and factors to ultimately prevent and cure the onset of Parkinson’s disease?

References


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