Pathophysiology of Schizophrenia: Impact of Cannabis Overuse Disorder on Neurobiology

Aina M. M. & Cindy Z

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Schizophrenia is a complex and severe psychiatric disorder that affects 1% of the whole world population. It is a type of psychosis in which the person is unable to discern between their own thoughts, ideas, and reality, according to scientists and therapists. Schizophrenia can be innate, a person can be born with the circumstance, or they can develop it overtime by having behaviors that increase their risk of suffering the disease. Cannabis overuse disorder, a type of drug abuse disorder, has been shown to chemically modify the structure of the brain, which matches with the formation of the brain of a person with schizophrenia. Therefore, the overconsumption of this drug can affect the neurobiology, leading eventually to the development of schizophrenia. This is done by affecting the neurotransmitters glutamate, dopamine and the endocannabinoid and tetrahydrocannabinol system. This review will corroborate the fact that cannabis overuse disorder affects several neurotransmitters in the brain, which can lead to anomalies in the neurotransmitter system and an increased risk of schizophrenia.

Keywords: schizophrenia, drug abuse, cannabis overuse disorder, glutamate, dopamine, endocannabinoid system, tetrahydrocannabinol system

Introduction

The first scientist to identify the symptoms of schizophrenia and state it as a disease was Emil Kraepelin in the 1850s. He named it dementia precox. In 1908, Eugen Bleuler investigated more into depth this concept and created the term "schizophrenia". He described it as a "group of psychosis having a variable and chronic course"[1]. Schizophrenia is a complex and severe psychiatric disorder that affects 1% of the whole world population[2]. Scientists and clinicians describe schizophrenia as a type of psychosis in which the person is not able to distinguish their own thoughts and ideas from reality. There are two types of symptoms, negative and positive. Negative symptoms are the functions that they stop doing, therefore: blunted emotions, alogia (reduction in words spoken), avolition (less motivation when setting goals or doing activities), anhedonia (decrease of the feeling of pleasure) and asociality. Positive symptoms are the ones the patient develops as the disease also does, for example: hallucinations (can be visual or auditory), delusions and disorganized thinking[3]. Patients who have developed schizophrenia due to the abuse of cannabis, tend to have more positive symptoms than negative[4].

Schizophrenia can be innate, a person can be born with the circumstance, or they can develop it overtime by having behaviors that increase their risk of suffering the disease. There are six main etiologies of schizophrenia which can be classified as: genetics, affected neurotransmitters, complications during pregnancy and birth, abnormal development of the brain, real life triggers (such as stress, losing a job or a traumatic experience) and drug abuse.

Firstly, there is not a single gene that causes schizophrenia, it is more probable that a combination of genes does[5]. Nevertheless, having combinations determined as the one's causing schizophrenia does not mean a person will develop the disease[6]. It is believed that schizophrenia runs in families so if, for instance, one of the parents suffers from the mental disorder it is very probable that their kids will develop schizophrenia. Scientists have shown this by comparing the genes of identical twins. They observed that if one of the twins had schizophrenia, the other twin has a 1 in 2 chance of suffering from it too. In non-identical twins, if one of the twins develops schizophrenia, the chance of the other twin is 1 in 8 for developing the disease7. However, general population has a chance of 1 in 100[5], therefore, the probability is notably less. It has also been researched families with schizophrenia which, when having an offspring, they pass the disease. In other words, if the progeny of a person has schizophrenia this may be in their genes, meaning that the offspring may eventually develop the disorder[7]. This raises the idea that genetics is one of several factors in charge of causing schizophrenia.

Abnormal brain development also increases the risk of developing schizophrenia. This can originate from an abnormal fetal development or a serious low weight during birth[8]. Neurotransmitters are chemicals responsible for neuron communication.

It is believed that people suffering from schizophrenia have in their brain abnormal amounts of neurotransmitters. For instance, serotonin is in charge of making a person feel pleasure. Sometimes, people with schizophrenia have lower levels of serotonin, therefore, this can explain why some people suffering from the disease suffer, at the same time, from depression[9].

Complications can occur during pregnancy and birth, making the human being to develop differently, for example, like occurs in preeclampsia. Preeclampsia is when the pregnant woman develops high blood pressure, high levels of protein in urine that indicate that the kidney is damaged (proteinuria), or other sign of organ damage. Some of the complications that can occur are fetal growth restriction, preterm birth and placental abruption[10]. When a baby is born in this condition, they have a higher risk of developing schizophrenia as there can be altered neuroimmune interactions. For example, umbilical and maternal levels of serum of tumor necrosis factor, a pro-inflammatory factor, are higher in preeclampsia. It has been shown that the tumor necrosis factor has an impact in the pathophysiology of schizophrenia[11].

Triggers are actions that can alter someone's system and, consequently, make them have a higher risk of developing the mental disorder. One example of a trigger is stress; life events that create a high level of stress, such as physical abuse, can make a person who is already at risk of developing schizophrenia more likely to suffer it[6].

This review will focus on drug abuse, specifically cannabis overuse and how it increases the risk of developing schizophrenia. Substance abuse can be defined as the excessive consumption of a material which, this excessive consumption, harms the organisms inside the body, making them alter their functions and activity[12]. This can lead to serious diseases which can be lethal or cause a challenging lifestyle. As the Epidemiological Catchment area study states, 47% of patients diagnosed with schizophrenia have had severe problems to drugs and substances during their lifetime[2]. Drugs have shown to play a role in converting the body more prone to developing psychosis if there is a dependability by the patient. However, it is important to highlight that this increase on risk of developing the mental disorder does not indicate that it is a direct cause to develop schizophrenia; it just makes someone more vulnerable to suffering from it as some specific parts of the body may be modified that are the same ones that make schizophrenia originate.

There are several ways of treating schizophrenia, the main two categories are therapy and medication. Most of the patients attend community mental health teams, which their goal is to provide day-to-day support and treatment and also are not receiving external treatment. People which have severe schizophrenic episodes may have to stay at a hospital or psychiatric clinic. A treatment that can be done at your own home or in a day care center is crisis resolution teams. This is specially done when someone experiences an acute and severe psychiatric episode.

Typical antipsychotics	Atypical antipsychotics
Shaking	Drowsiness
Trembling	Weight gain
Muscle twitches	Lack of sex drive
Muscles spasms	Blurred vision
	Constipation
	Dry mouth

Table 1 Symptoms treated by typical and atypical psychotics

Other types of therapies are talking therapies, which have different groups: cognitive behavioral therapy (CBT), family therapy and arts therapy. CBT helps the patient to identify the thinking patterns that are making them have the undesired feelings or behaviors. Furthermore, it helps you change your thoughts in that moment for more realistic and useful ones. Family therapy aims to provide support for the person suffering from the disorder and the people which are close to them. Lasty, art therapy is a way in which the patient expresses their thoughts or feelings in a creative way; for some people this type of non-verbal situation makes their process of explaining and describing their feelings easier[13].

Antipsychotics are medications which work by blocking the effects that the chemical dopamine has or other chemicals on the brain needed to reduce the psychotic episodes. They reduce the feelings of anxiety or aggression, however, to decrease other symptoms like hallucinations or delusional thoughts may take some weeks or days. There are two types of antipsychotics: typical antipsychotics, which are the ones developed in the 1950's and atypical antipsychotics, developed in the 1990's. They both have side effects, nevertheless, they differ in some[13]:

Despite the existing limitations on the understanding of the neurobiology of patients with schizophrenia, in 2023 new treatments are being created which could work efficiently. Brilarozaxine is a dopamine-serotonin stabilizer that acts on both dopamine and serotonin receptors. Reviva Pharmaceuticals made an experiment to measure the effectiveness of brilarozaxine by comparing it to patients given placebo over four weeks using the Postive and Negative Symptoms Assessment (PANSS). This means that a 30-item physician evaluates the patients' schizophrenia symptoms (both positive and negative).

Furthermore, Newron Pharmaceuticals is experimenting with evenamide, which blocks glutamate modulation and voltage-gated sodium channels that could modulate repetitive neuron firing without impairing normal neuronal excitability. They also use PANSS over four weeks to measure the effectiveness.

Sunovion Pharmaceuticals is currently investigating with ulotaront, which is an agoinst of the trace amine-associated receptor 1 (TAAR1) and serotonin 5HT1A receptors. This offers a different approach from the traditional antipsychotics that target dopamine receptors. PANSS is also used over six weeks

Search Tools	Specific Terms
PubMed	Psychosis
Google Scholar	Psychosis and cannabis
PubMed	Schizophrenia and cannabis
PubMed	Effects of cannabis in the brain
Google Scholar	Cannabis
PubMed	Etiologies of schizophrenia
Google Scholar	Schizophrenia
Google Scholar	Drug abuse and psychosis
PubMed	Dopamine and psychosis
PubMed	Glutamate and psychosis
Google Scholar	Drugs and genetics

Table 2 Search tools used to search specific terms related to the research question.

to measure the effectiveness of ulotaront.

Acadia Pharmaceuticals is measuring the effectiveness of pimavanserin which is a serotonin inverse agonist and antagonist that preferentially targets 5-hydroxytryptamine (5HT2A) receptors which are thought to have a role in psychosis and schizophrenia. They use the Negative Symptom Assessment-16 (NSA-16) which measures the negative symptoms of schizophrenia (communication, emotion/affect, social involvement, motivation and retardation). Pimavanserin has FDA approval under the brand name Nuplazid for the treatment of Parkinson's disease psychosis [14].

The hypothesis of this review is that cannabis overuse disorder does have an impact on the brain that will affect several neurotransmitters and, therefore, create abnormalities in the neurotransmitter system that will make someone more likely to develop schizophrenia.

Methodology

The engines used to conduct this research were PubMed and Google Scholar to search specific terms related to the research question (see Table I). The selection and exclusion criteria for choosing papers were: i) published between the years 2005 and 2023, ii) one scientist or more have written the paper, iii) papers written in Spanish or English, iv) studies conducted both with animals and humans, v) the article has been downloaded and cited many times, vi) the title of the paper contains all the keywords that are being searched, vii) hypothesis is clearly stated and contains nearly all keywords. In order to avoid potential biases, all the information extracted from different sources is cited, the quality of the sources was investigated and different perspectives from the research question were also evaluated and analyzed.

Results and Discussion

Cannabis Overuse Disorder and Schizophrenia

Cannabis is the third most used substance worldwide, behind alcohol and tobacco. Its properties are due to one cannabinoid: delta-9tetrahydrocannabinol (THC). The legal use of cannabis varies internationally, however, in the last decades the use of marijuana has increased. Cannabis use disorder refers to a dangerous and problematic use of the drug. In 2016, it was estimated that 22.1 million people suffered from this disorder. Several studies discovered that most of these people that developed this addiction were around 22 years old [15]. There are groups of ages that show higher rates of use of cannabis:

18-25 years: 35.4%
26-49 years: 21.7%
12-17 years: 13.2%
65+ years: 5.1%
(16)

As it will be mentioned in points 3.2.1 and 3.2.2, due to the effects on dopamine and glutamate that marijuana has in the brain, cannabis can decrease someone's level of attention, memory, learning and decision making in the short term. However, it has been shown that an excessive use of cannabis in adolescence or early adulthood can damage the development of the brain. For example, some outcomes can be poor school performance, dropouts, welfare dependence, unemployment, and low life satisfaction [16]. Another study conducted by Terrie Moffitt, a psychologist at Duke University, used participants of ages 13, 18, 21, 26, 32 and 38. They discovered that marijuana tended to decrease the intelligence quotient of the ones consuming it. The users that consumed this drug the most, reported an intelligence quotient of six points [17]. The reason teenagers are more damaged by the use of cannabis is because their brain is still developing until the early or mid 20s. Therefore, during this period of development, the brain is believed to be very sensitive to damage provoked by drug exposure. Furthermore, the frontal cortex, the part in charge of planning, judgement, decision making and personality, is one of the last regions to fully develop [16].

Another study done in 2013 by Rocío Martín-Santos at the University of Barcelona reviewed several studies of cannabis overuse and the effect that it has on the brain. They saw that there is enough evidence to prove that the brain suffers from structural abnormalities and altered neural activity [18].

The diagnosis of cannabis addiction, according to DSM-4, includes irritability, aggression, anxiety, sleep difficulty, decreased appetite or weight loss, restlessness, depressed mood. There are also physical symptoms such as tremors, sweating and fever [17].

There are some symptoms of schizophrenia that are similar

DSM-5 Diagnosis of schizophrenia	Effects of cannabis overuse
For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).	Cannabis affects the levels of dopamine, which is responsible of the rewarding system and involved in the process of learning. Therefore, if dopamine is altered academic/working failure occurs. Also, marijuana overuse in adolescents damages the frontal cortex, making their decisions, personality, planning and judgments incoherent, therefore, different disturbances in their daily tasks can occur.
A dysphoric mood that can take the form of depression, anxiety, or anger; a disturbed sleep pattern (e.g., daytime sleeping and nighttime activity); and a lack of interest in eating or food refusal.	The diagnosis of cannabis overuse includes depression, anxiety, anger, disturbed sleep pattern and weight loss or decreased appetite. Also, glutamate levels are affected, which makes the brain not to process emotions the correct way.
Cognitive deficits in schizophrenia are common and are strongly linked to vocational and functional impairments. These deficits can include decrements in declarative memory, working memory, language function and other executive functions, as well as slower processing speed.	As it was mentioned before, the levels of dopamine are affected as also some parts of the brain (mainly focusing on the frontal cortex) can be damaged and become abnormal. Both of these effects make all of the deficits mentioned in the DSM-5 occur.

Table 3 Symptoms in Common between Schizophrenia and Cannabis Overuse

to the cannabis ones, meaning that marijuana overuse can alter the brain to make it more likely to develop schizophrenia:

It is very important to clarify that the consumption of excessive amounts of cannabis can make someone more likely to develop schizophrenia, however, it cannot directly cause schizophrenia. A study conducted in 2021, researched about the genetic relationship between the addiction of cannabis and schizophrenia. The results showed that people which had cannabis overuse disorder were significantly associated with a higher risk of developing schizophrenia. They also tested tobacco users and people that were not active cannabis consumers[18]. Another study states that approximately 1 in every 4 individuals with schizophrenia is diagnosed with cannabis overuse disorder. Furthermore, consistent cannabis users are two times more likely to develop psychosis; for addicted people this risk increases to four. It also mentions that it is estimated that in North America and Europe one-third of patients that report a first psychotic episode are diagnosed with a regular cannabis use[19].

Neurotransmitter Systems in Cannabis Overuse and Schizophrenia

Dopaminergic System

During centuries it has been discussed what the function of dopamine is. However, in the 90s they encoded phasic dopamine as *reward prediction errors* (RPEs). They did this by studying the rewarding respond of the cell to unexpected stimuli from a future reward. They contrasted this with the neutral respond that cells had when the reward was expected. RPEs are also related to the process of learning, therefore, it is known that dopamine has a role when learning. To confirm this surely, they went through optogenetic manipulations and they confirmed that dopamine does have a role[20]. In summary, dopamine more so makes up what is collectively known as the brain's reward system. Nevertheless, scientists have yet to discover whether dopamine functions with the predicted or motivational activities, as both are usually accomplished together24.

The dopamine hypothesis states that an alteration in the production of dopamine could cause an important brain damage which could make someone more likely to develop schizophrenia[21]. One of the most important studies that demonstrated this showed that by administering amphetamine or other substances which increase the concentrations of dopamine in the brain caused psychotic symptoms. These symptoms are the same as the patients with schizophrenia. To complete the study, they used other drugs as alpha-methyl-para-tyrosine that decrease the psychotic symptoms as it also depleted dopamine levels. More evidence was discovered in the 1970s as they realized that the medicine they were using to treat patients, antipsychotic drugs, were directed to cure dopamine receptors[22].

More evidence of the relation between dopamine and schizophrenia came thanks to the advances in technology, which gave in vivo images of dopaminergic function in the brain. This is thanks to Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT)[22], which are molecular imaging techniques that enable a real characterization and measurement of biologic processes using a never

seen affinity and specificity molecular probes[23].

A study conducted by Urban and companions used volunteers to see if cannabis has an effect on dopamine levels. They chose 16 psychiatrically healthy cannabis smokers participants, more specifically 1 woman and 15 men of the age 27.3 ± 6.1 years. Then 16 control subjects, 2 of them were woman and 14 men of the age 28.1 ± 6.7 years. They made two positron emission tomography scans before and after the injection of 0.3 mg/kg of intravenous d-amphetamine. The percentage change of raclopride binding (selective antagonist on D2 dopamine receptors) after the injection of amphetamine in subregions of the striatum were compared between groups.

Cannabis consumers that they tested had an average consumption of 517 ± 465 estimated puffs per month, which indicates a mild to moderate cannabis dependance. They concluded that cannabis does have an effect on the dopamine system, however, compared to other drugs addictions (such as cocaine) it is less harmful. It only damages the system in long or earlier consumptions. Therefore, adolescents and people with cannabis overuse disorder are more likely to have altered dopamine levels[24].

Glutamate

Glutamate is one of the most abundant proteins in the system. Their role is involved in nutrition, metabolism and signaling. In metabolism and nutrition, it is fundamental for the synthesis of important molecules. In the nervous system it is determined to be the major excitatory neurotransmitter. Gamma-aminobutyric acid (GABA), its product, is the most important inhibitory neurotransmitter[25].

The glutamate hypothesis of schizophrenia originated in the 1990s by several observations on antagonists of the N-methyl-D-aspartate glutamate receptors (e.g., phencyclidine and ketamine), develop the same positive and negative symptoms in healthy volunteers than people with schizophrenia. Around the 1980s scientists observed that PCP created effects similar to the symptoms of schizophrenia in healthy volunteers and in schizophrenic volunteers it made their already developed symptoms worse. Thanks to this discovery, twenty years later, they created a relation between the effects of PCP to the glutamatergic system. Consequently, this was the key discovery to the formation of the glutamate hypothesis[26].

In addition, studies conducted in humans suggest that chronic cannabis use reduces the levels of glutamate in cortical and subcortical brain areas. Studies done with animals demonstrate that this drug decreases glutamate synaptic transmission, which affects glutamate release, inhibiting receptors and transporters function, reducing enzyme activity and disrupting glutamate synaptic plasticity after a long exposure[27].

Apart from the effects on the dopamine and glutamate levels, chronic cannabis use is also associated with changes in stress responsivity. It was proved that the stress peptide corticotropin-releasing factor (CRF) levels increase in the central nucleus of the amygdala in a study done with mice by administering an amount of cannabis. Also, cannabis users show a dysregulation of stress responsivity. Studies show that humans addicted to marijuana have both blunted and hyperactive stress responses[28]. Therefore, this demonstrates that the effects that cannabis overuse disorder has on dopamine and glutamate levels creates symptoms which are also present in patients with schizophrenia.

Tetrahydrocannabinol and the endocannabinoid system

Tetrahydrocannabinol (THC) is the most important (from 113 cannabinoids) psychoactive component in cannabis. Its chemical formula is delta-9terahydrocannabinol[29]. THC, back in the 1966, was determined to be responsible or the intoxicating properties of cannabis. These include alterations in mood, perception and cognition[30].

The endocannabinoid system (ECS) is a vast network of chemical signals and cellular receptors that are densely packed and distributed in humans' brains and bodies. Their function is to control the levels and activity of most of the neurotransmitters[31]. ECS primarily influences neuronal synaptic communication and affects biological factors via an array of actions throughout the nervous system. It influences neuronal synaptic communication and affects biological functions (i.e., eating, anxiety, reproduction, memory...) via an array of actions throughout the nervous system[32]. To demonstrate the roles of the ECS signaling in the nervous system, researcher Elphick explained this with past research on non-mammalian model animals (for instance, Hirudo medicinalis, Ciona interstinalis, Danio rerio)[33].

To regulate this, the system provides feedback, turning up or down the activity of the system that needs to be correctly adjusted. This can be hunger, temperature, or alertness[31]. Research shows that the amygdala is the brain area regulating appetite with response to emotions. It is usual that people with depression or other mental disorders have altered food habits (it involves both obesity and anorexia between others)[34]. Some of the neurotransmitters that are found in the amygdala are y-aminobutyric acid, glutamic acid, N-methyl-D-aspartate, dopamine and 5-hydroxytriptamine[35]. The thermoregulation system, found in the hypothalamus, sweat glands, skin and the circulatory system, controls the body temperature[36]. The hypothalamus releases different neurotransmitters, these include GABA, glutamate, kisspeptin, opioids, dopamine, norepinephrine and serotonin[37]. The reticular activating system, found in the midbrain, pons, medulla and part of the thalamus, enables the body to pay attention when it is required[38]. The neurotransmitters vary because of the variety of brain parts, therefore, in the midbrain dopamine is found[39], in the medulla the classical neurotransmitter catecholamines[40] and the thalamus the neurotransmitters glutamate, GABA, dopamine and serotonin and at a less frequent extent noradrenaline and histamine[39].

The ECS is comprised of endogenous cannabinoids (endocannabinoids), cannabinoid receptors and proteins that transport,

synthesize and degrade endocannabinoids. When referring to cannabis, it contains several bioactive compounds. Many of the psychoactive effects are associated through the interaction of THC, however, the major psychotropic constituent of cannabis occurs though the interaction with the cannabinoid receptors[41]. Cannabidiol (CBD) is another component of cannabis, which can be present in different levels, that also interacts with the ECS and with other neuromodulatory systems, such as the brain-derived neurotropic factor[42]. CBD can either enhance or inhibit activation of its binding site target. Cannabidiol blocks the activation of the equilibrative nucleoside transporter (GPR55, a novel cannabinoid receptor that increases intracellular calcium and inhibits M current[43]) and the TRP cation channel subfamily (glycine receptors TRPM8, that are channels that are essential for the detection of environmental cold temperatures in the somatosensory system[44]). It also enhances the activity of serotonin 1A receptor, glycine receptors $\alpha 1$ and $\alpha 3$ and TRPA1[45].

CBD can also be used as a treatment for psychosis. The ECS system is related with schizophrenia as the administration of THC appears to make patients develop some symptoms of schizophrenia. Endocannabinoid levels are altered in schizophrenia and change during treatment with antipsychotic drugs[41]. Studies in which healthy volunteers were administered THC showed acute psychotic symptoms and transient dose-related cognitive impairments, such as working memory and control of attention. However, treatment done with CBD has been shown to mitigate the symptoms created by THC. Studies done with animals determined that CBD has similar behavioral responses to those in an atypical antipsychotic drug[46]. In summary, THC can have adverse effects related to schizophrenia (psychosis) regardless on your mental health conditions, whereas CBD has not been suggested to make any schizophrenia symptoms worse[47].

THC acts in a certain way through D3 receptors, with an interaction between cannabinoid receptor type 1 (CB1R) and dopamine D(3) receptors (D3R). D3R agonist, PIPAT, increases the motor effect of THC, but the D3R antagonist GR103691 is capable of reducing the motor effect of THC. THC modifies the endocannabinoid system by upregulating CB1 in the prefrontal cortex. NAPE-PLD cDNA levels are decreased in the prefrontal cortex and striatum. Furthermore, it upregulates the gene expression of the fatty acid amide hydrolase (FAAH) enzyme in the prefrontal cortex and dorsal striatum. Interestingly, THC has biphasic effects on the survival of nigral neurons (dopamine producers), as it exerts neurotoxic and neuroprotective effects[48].

Interaction between drugs and genetics

It has been proven that there are people who, because of their genome, they are more likely to become addicted to a certain group of substances. Variations in DNA result in gene variants that, therefore, change their initial (normal) function to an incorrect one[49]. High exposure to the use of drugs can also alter gene expression as the brain accommodates itself because of the constant rewards the brain receives[50]. It is affected through changing the concentration of transcription factors in the nuclei of cells. They alter neurotransmission at synapses in the brain and, therefore, cause biochemical reactions that will end up reaching the nucleus. When they arrive to the nucleus, these signals affect gene expression[51].

In addition, epigenetics (where the sequence does not change, however, the environment interacts with the chemicals that attach on top of the genome that, consequently, modify the expression of the genes) can also be affected. This drug induced epigenetic adaptations make serious changes in the function of the brain which contribute to life-long, drug-related behavioral abnormalities that lead to the analysis of addiction[52]. Some examples of the alterations produced are histone acetylation, phosphorylation and methylation levels and DNA methylation levels[50].

The changes in the number of copies that DNA suffers is known as copy number variants (CNVs) and result from the deletion (del) or duplication (dup) of a relatively large genomic region. Consequently, the modification of one or more genes in a region can increase the risk for diseases. Multiple rare CNVs are established as risk factors for psychiatric disorders like schizophrenia, mental retardation and autism. There are eight CNVs that have a strong effect on disease risk and have been associated with psychiatric disorders:
Two CNVs impact single genes: 2p16.3 del (neurexin 1 [NRXN1]) (35) and 7q36.3 dup (vasoactive intestinal peptide receptor 2 [VIPR2]) (36).
These alter the dosages of many genes: 1q21.1 del/dup (34 genes) (37–41), 3q29 del (19 genes) (34, 37, 42), 7q11.23 dup (25 genes) (37, 43, 44), 15q11.2 dup (70 genes) (39, 45), 15q13.3 del/dup (12 genes) (38, 39, 46), 16p13.11 dup (47, 48) (8 genes), 16p11.2 del/dup (29 genes) (49–53), 17q12 del (18 genes) (54), and 22q11.2 del/dup (53 genes) (45, 55)[53].

A study conducted by Nannini et. al in 2022 was focusing on the DNA methylation caused by marijuana use in young adults. To do this research they used an already existing methodology in another paper: CARDIA study design. In this experiment, they recruited 5115 black and white participants from 1985 to 1986 from the ages 18 to 30 from across the United States. They measured marijuana by asking specific questions to the participants such as "Have you ever used marijuana?" They also considered four variables when looking if someone had ever consumed marijuana or in the last 30 days. Two binary marijuana variables indicated if someone ever consumed cannabis and used it in the last 30 days. Another continuous variable quantified how many days (in the last 30 days) had someone consumed marijuana. The last estimated continuous variable indicated the quantity of years that cannabis was used. The results indicated that marijuana consumption can change the genetics of someone. GrimAge is a biomarker of specifically

seven DNA methylation surrogates, which seven of these have been related with components of the endocannabinoid system, such as, leptin, GDF15, cystatin C and PAI1. They observed correlations between some GrimAge surrogate biomarkers of blood plasma proteins and marijuana. This suggests that DNA methylation is related to marijuana use by the changes of these specific plasma proteins[54].

As this study states, genetics can be modified by cannabis overuse disorder, altering the production of specific enzymes[55]. A person with schizophrenia also has genes that are slightly modified which are only expressed if exposed to certain scenarios as mentioned in the introduction. One of these scenarios is the exposure to drugs; therefore, if a person which, based on their genetics, is more likely to develop schizophrenia consumes cannabis, the drug will modify specific genes that will exponentially increase the risk of developing schizophrenia.

Furthermore, as the study of Filomena Mazzeo and Rosaria Meccariello states, if the progenitors of a person were addicted to a cannabis during and before birth, their genetics may have changed, making the offspring likely to have this methylation in their DNA that will make their risk to be addicted to cannabis higher. This means that the offspring will be more likely to become addicted to cannabis and, if the infant has the altered genes of schizophrenia, will eventually develop schizophrenia[56].

Conclusion

In the results part, it was demonstrated that a constant overuse of cannabis may alter the brain chemistry making someone more likely to develop schizophrenia. However, suffer from cannabis overuse disorder does not always mean that that person will develop schizophrenia. It has been shown that 15%-30% of people with this disorder develop paranoia and 3%-27% hallucinations. There are other causes for developing schizophrenia that have been discussed in the introduction of this review. For example, certain triggers, like job loss, can potentially lead to the development of brain abnormalities in individuals who are already predisposed to schizophrenia due to their unique brain structure. Therefore, this trigger has made the brain to fully start developing the disorder. It is crucial to consider that these factors do not directly cause the development of schizophrenia; instead, they contribute to the development of brain abnormalities that can lead to the evolution of schizophrenia. In this study it was explained the relationship of cannabis overuse disorder and schizophrenia. This literature review highlighted the relationship between cannabis overuse disorder and schizophrenia by explaining neurotransmitter deficits common to both. The limitations of this research are not being able to use papers written in any other language apart from Spanish or English and not using every paper which researched about schizophrenia and cannabis. Future research must be done in order to discover more the causes of schizophrenia as it will save many lives of people who suffer the disease.

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