

September 2022

Associations Between Cannabis, Psychosis, and Schizophrenia in Adolescents

Lauren Moment

University of Colorado - Denver, lauren.moment@ucdenver.edu

Follow this and additional works at: <https://scholars.fhsu.edu/aljsr>



Part of the [Behavioral Medicine Commons](#), [Biological Psychology Commons](#), [Chemical and Pharmacologic Phenomena Commons](#), [Child Psychology Commons](#), [Medical Pathology Commons](#), [Medical Pharmacology Commons](#), [Pathological Conditions, Signs and Symptoms Commons](#), [Pharmacology Commons](#), [Psychiatric and Mental Health Commons](#), [Substance Abuse and Addiction Commons](#), [Toxicology Commons](#), and the [Weed Science Commons](#)

Recommended Citation

Moment, Lauren (2022) "Associations Between Cannabis, Psychosis, and Schizophrenia in Adolescents," *Academic Leadership Journal in Student Research*: Vol. 6, Article 1.

Available at: <https://scholars.fhsu.edu/aljsr/vol6/iss1/1>

This Article is brought to you for free and open access by the Peer-Reviewed Journals at FHSU Scholars Repository. It has been accepted for inclusion in Academic Leadership Journal in Student Research by an authorized editor of FHSU Scholars Repository. For more information, please contact ScholarsRepository@fhsu.edu.

Associations Between Cannabis, Psychosis, and Schizophrenia in Adolescents

Cover Page Footnote

I would like to acknowledge my faculty mentor, Dr. Erik Oleson and committee member Dr. Michael Zinser, for their leadership and guidance on this honors project.

Associations Between Cannabis, Psychosis, and Schizophrenia in Adolescents

Lauren Moment, B.S., M.P.A, PMP©

Department of Psychology

University of Colorado – Denver | Anschutz Medical School

Abstract

The effects of cannabis use on the brain, mind, and body have been studied for decades. The developing brain, particularly the adolescent and young adult brain, undergoes critical development that makes it especially susceptible to the effects of cannabis use. Among the adverse effects of cannabis use in adolescence and young adulthood, psychosis, and psychotic disorders (e.g., schizophrenia) have been examined. The association of cannabis use with schizophrenia was first elucidated in a Swedish study of army conscripts. Specifically, conscripts reported their cannabis use exposure and were followed longitudinally to assess the emergence of schizophrenia. The authors found that those who reported persistent cannabis use during adolescence had higher rates of schizophrenia diagnoses.

Notwithstanding this correlation, a causal relationship has not yet been established between adolescent cannabis use and schizophrenia. Some believe that in the premorbid phase of schizophrenia, one may self-medicate with cannabis, accounting for the correlational

relationship. However, this evidence is not supported by the literature. Prolonged, frequent use of exogenous cannabinoids such as phytocannabinoids and synthetic cannabinoids perturb the endocannabinoid system, particularly during the critical period of adolescence. Many researchers believe this perturbation contributes to psychosis and the pathogenesis of schizophrenia.

Keywords: cannabis, schizophrenia, psychosis, adolescence

Associations Between Cannabis, Psychosis, and Schizophrenia in Adolescents

The relationship between cannabis use, psychosis, and schizophrenia has been studied for decades. As cannabis is the most utilized mood-altering drug in the United States and the world (Abush et al., 2018), many researchers are interested in its effects on mental health. However, despite the extensive literature on cannabis, psychosis, and schizophrenia, the causal nature of these interrelationships remains unclear. Indeed, this relationship involves other factors that may confound it. As stated previously, cannabis is the most widely used drug in many developed and underdeveloped societies. However, its public health and psychiatric effects are not widely understood and are the subject of intense polemics. Cannabis is derived from the female plant of *cannabis sativa*. It contains over 400 cannabinoids, one of which is the primary psychoactive component delta-9 tetrahydrocannabinol (THC). From a pharmacological perspective, a cannabinoid is a category of chemical compounds such as phytocannabinoids, synthetic cannabinoids, and endogenous cannabinoids that bind to CB1 and CB2 receptors (Oleson & Cheer, 2012).

Cannabis also includes cannabidiol (CBD), which does not have psychoactive properties and has been purported to counterbalance the effects of THC. However, THC produces several pharmacological effects in humans and animals (Adams & Martin, 1996). Over the last few decades, progress has been made in categorizing cannabinoids and the cannabinoid receptors in the endocannabinoid system, which communicate with other messenger systems at the cellular level. Although THC will be discussed most extensively throughout this review, the primary purpose is to examine the association between cannabis, psychosis, and schizophrenia. Although there appear to be interrelationships, there are critical differences between schizophrenia and cannabis-induced psychosis (CIP). As these relationships were analyzed, the following research question was asked: For those who use cannabis in adolescence, do they experience more instances of cannabis-induced psychosis, and does it lead to higher occurrences of schizophrenia?

Methods

Google Scholar and PubMed were the databases utilized to conduct this literature review. Upon initial search, the terms "cannabis-induced psychosis" AND "schizophrenia" were used. This search yielded 237,908 results. The results were narrowed to 1,908 by clicking on "adolescence." PubMed was chosen due to its public interface searchable via MEDLINE and the National Library of Medicine. It is the most comprehensive database for biomedical literature. Google Scholar was selected because it shows articles within search parameters and articles related to topics of interest. These terms yielded articles about schizophrenia and cannabis-induced psychosis.

Differences Between Schizophrenia and Cannabis – Induced Psychosis

One of the significant differences between schizophrenia and CIP is the duration of symptoms. Psychosis can be a symptom of many mental illnesses, whereas schizophrenia is a chronic illness that requires a lifetime of treatment (American Psychiatric Association, 2013). In schizophrenia, symptoms persist despite drug abstinence. However, symptoms in CIP abate or are reduced in abstinence. People with schizophrenia may test positive on urine toxicology if they engage in cannabis consumption. However, a positive toxicology screen in an individual with CIP indicates a clear timeline of the time of last drug ingestion. This timeline will also indicate if psychosis is closely related to the cannabis intoxication/withdrawal effects.

One of the features of CIP is the sudden onset of mood lability and paranoid symptoms. These symptoms usually occur within a week of use. Therefore, criteria for CIP must exclude the diagnosis of schizophrenia. These symptoms should also be more than anticipated intoxication and withdrawal symptoms. In terms of the appearance of symptoms, schizophrenia appears in the absence of cannabis use. With CIP, symptoms only occur during periods of heavy (2 grams per day or more) use. In addition, CIP has traditionally been concomitant with fewer negative symptoms than schizophrenia. Nevertheless, in the absence of a clear timeline of cannabis use, distinguishing schizophrenia from CIP may be problematic. This may lead to an incorrect intervention. Many of the clinical features of schizophrenia share many overlapping characteristics with CIP. However, in comparison with schizophrenia, CIP has been recognized to show more mood symptoms.

One of the most salient features of CIP is insight. In schizophrenia, there is less insight into their psychotic state. However, there is more awareness of CIP. Insight is the most discerning characteristic of CIP due to the cognizance of one's clinical condition, greater disease insight, and the ability to identify symptoms as a manifestation of substance use. The

existence of much more rapidly declining positive symptoms is also a distinguishing factor of CIP. Lastly, in schizophrenia, disorganized thought-form such as loose associations and tangential or circumstantial speech is present. However, with CIP, thought is more sequential and organized. Although there are prominent differences, both syndromes can affect adolescents.

Associations Between Cannabis, Psychosis, and Schizophrenia in Adolescents

Prolonged cannabis use has been correlated with schizophrenia (Lubman et al., 2015). The neurological basis of this association, while not fully understood, points to the use of cannabis among those who are vulnerable to schizophrenia leading to psychosis and cognitive impairments, particularly when use begins in adolescence. The endocannabinoid system (ECS) plays a pivotal role in brain development. Therefore, it is plausible that early and frequent use of cannabis perturbs the neuromaturational processes occurring in this system during adolescence, leading to psychosis and schizophrenia. White matter development and synaptic pruning are two aspects that have been identified as being inversely impacted by cannabis exposure during the critical period of adolescence (Harley et al., 2010).

According to Zuurman et al. (2009), cannabis disrupts the nervous system in multiple ways. This disruption may result in perceptual distortions, relaxation, euphoria, increased sensory perception, anxiety, hunger, and dizziness. Quickfall and Crockford's (2006) study examined brain function during acute THC intoxication and discovered increased cerebral blood flow in the limbic, paralimbic, frontal, and cerebellar regions associated with use. This study found that there are biochemical effects due to the opposing characteristics of THC and CBD. Indeed, other researchers have found that THC produces anxiety and cognitive and perceptual disturbances while CBD produces anxiolytic effects (Zuardi et al., 1993; Bergamaschi et al., 2011) and can have antipsychotic properties (Zuardi et al., 2006). These studies have also indicated that CBD can thwart the effects of THC (Zuardi et al., 1982). Although the association between the biochemical effects of the adolescent brain and Cannabis sativa is still under investigation, many articles in the literature point to this relationship and the etiology of schizophrenia.

Etiology of Schizophrenia

Schizophrenia is one of the most debilitating diseases in psychiatry. One of the many reasons for its debilitating symptoms is a misunderstanding among the psychiatric and lay community regarding its cause and effective treatments. According to the Diagnostic and

Statistical Manual (DSM 5), schizophrenia may consist of disorganized speech, disorganized and catatonic behavior, delusions, hallucinations, and negative symptoms (American Psychiatric Association, 2013). Two or more of these symptoms must be present for one month or more to diagnose the disorder. The construct of schizophrenia in the DSM 5 has been proven to have high reliability and validity.

The cause of schizophrenia, despite over a century of studying its pathogenesis, etiology, pathophysiology, and pharmacological outcomes, is unknown. However, a significant amount of evidence has suggested that it is associated with excessive stimulation of striatal dopamine (DA) D2 receptors; deficient stimulation of prefrontal D1 receptors; and alterations in prefrontal connectivity involving glutamate (GLU) transmission involving N-methyl-D-aspartate (NMDA) receptors (Laruelle et al., 2003). In addition, postmortem studies have suggested abnormalities in the expression of GLU-related proteins (Laruelle et al., 2003); however, these studies have yet to be reproduced. Clinical studies have also suggested that schizophrenia features low cerebrospinal fluid homovanillic acid, which is a measure that also indicates low DA activity in the prefrontal cortex (PFC).

Further evidence supporting the role of dopamine in schizophrenia derives from the efficacy of dopaminergic stabilizers in treating schizophrenia. Dopaminergic stabilizers have been shown to reestablish social behavior in rat models (Brisch et al., 2014). These studies have also shown that cognitive deficits associated with cannabis use are associated with DA decline in the PFC observed in schizophrenia. For example, in a survey of adolescents after 12 hours of abstinence from cannabis, those who used more than once per week had considerably poorer performance on several measures of cognitive function reflecting attention, spatial working memory, and learning (Harvey et al., 2007). These analyses suggest that aspects of adolescent cognitive function are autonomously related to the regularity of cannabis use beyond acute intoxication. These deficits also include executive functioning, language, processing speed, inhibition of attention, and sensory processing. The PFC is particularly concomitant with working memory. Auditory processing is also an impairment in those with schizophrenia. According to the literature, adolescent brain development is particularly vulnerable to exogenous insults.

Adolescent Brain Development

Adolescence is an important stage in cognitive and behavioral development that features significant neuromaturation. This maturation includes substantial changes in all neuronal domains that affect behavior, cognition, and affect (Steinberg, 2007). Areas of the brain that

develop during adolescence contribute to the ability to perform complex psychological tasks. During this critical stage of development, the transformation of brain regions influences cognition, sensorimotor systems, and motivation. This period involves synaptic pruning of the cortical synapses, which leads to a diminution in cortical gray matter and increased myelination (Giedd et al., 1999; Paus, 2005). The volume of cortical grey matter follows an inverted U-shape during this period, meaning that most of the region's volume that develops earliest is in areas of the brain responsible for cognitive functioning. This development occurs during adolescence and into early adulthood (Giedd et al., 2009). Many researchers assert that disjunctions among these developing regions render adolescence a critical period that involves increased susceptibility to mental health disorders such as schizophrenia (Spear, 2000; Steinberg, 2005). It is also a period of an increased likelihood of disjunctions in the endocannabinoid system for adolescents and young adults if THC is used.

The endocannabinoid system plays a critical role in neurodevelopment and neuromaturation. The ECS is comprised of two G-protein-coupled cannabinoid receptors (CB1 and CB2), endocannabinoid ligands, 2-arachidonoyl ethanolamide [2-AG], and the enzymes involved in amalgamation and degradation (De Petrocellis & Di Marzo, 2009). The CB1 receptor is expressed more often than other G-protein coupled receptors in the brain. This arbitrates the CNS effects of cannabis; however, the CB2 receptor plays a role in numerous other physiological systems, particularly in the immune system (Svíženská et al., 2008). Furthermore, CB1 receptors are located presynaptically, where initiation by endocannabinoids can constrain conduction in GABAergic and glutaminergic synapses (Freund et al., 2003). Thus, the ECS is critical in maintaining the balance between inhibitory and excitatory neuronal action. Also, CB1 inhibition of glutaminergic neurotransmission and regulation of glutamate-induced excitotoxicity may be the principal mechanism by which cannabinoids exert neuroprotective influence (Marsicano et al., 2003).

Cannabinoid receptors and endogenous cannabinoids develop early in the brain. This development includes the production and distinction of progenitor cells, neuronal migration, axonal pathfinding, and glial cell data (Fride, 2008; Harkany et al., 2008; Díaz-Alonso et al., 2012). Furthermore, there is growing evidence that the ECS develops during adolescence (Galve-Roperh et al., 2007; Malone et al., 2010; Galve-Roperh, 2012). Although the role of the ECS in adolescent neuromaturation has yet to be fully discovered, recent studies show increased CB1 density during adolescence (Bossong & Niesink, 2010).

Exogenous cannabinoids affect the functioning of the ECS, and researchers purport that cannabis use during adolescence may represent a disruption of this critical period of

development (Bossong & Niesink, 2010). Specifically, it may lead to enduring impacts that increase the likelihood of psychopathology (Bossong & Niesink, 2010; Downer & Campbell, 2010; Malone et al., 2010; Caballero & Tseng, 2012). Most importantly, cannabinoid-related disruptions in the ECS are positively correlated with schizophrenia (Galve-Roperh et al., 2009; Parolaro et al., 2010; Ferretjans et al., 2012). The endocannabinoid system regulates the generation and specification of neural cells during the early postnatal stages of brain development. In addition, it regulates neural cell maintenance and neuroprotection in the mature brain (Galve-Roperh et al., 2009).

In the developing adolescent brain, CB1 receptors facilitate neuronal migration and axonal pathfinding and the production of glial cells, including astrocytes and oligodendrocytes. There are two plausible mechanisms by which prolonged cannabis exposure during adolescence might disturb the processes of the endocannabinoid system and modify brain development: (1) by interfering with processes of synaptic pruning (red pathway); and (2) by altering the development of white matter (blue pathway).

In those with schizophrenia, deviations in CB1 binding have been found in frontal regions, including prefrontal and anterior cingulate cortex as well as in the ventral striatum (Zavitsanou et al., 2004; Newell et al., 2006; Eggen et al., 2010; Wong et al., 2010; Ceccarini et al., 2013). Some researchers have suggested that augmented receptor binding may intensify psychotic symptoms in schizophrenia (Wong et al., 2010; Ceccarini et al., 2013). Researchers have also shown that those with schizophrenia have genetic differences in the components of the ECS and variations in endocannabinoid levels in the cerebrospinal fluid (CSF) and blood (Ferretjans et al., 2012). Nonetheless, anomalous activity in the ECS may explain problems in recollection and academic retention associated with adolescent cannabis use, particularly THC (Sullivan, 2000; Marsicano & Lafenêtre, 2009).

The ECS consists of endogenous cannabinoids, enzymes, and cannabinoid receptors (Mackie, 2008). Although researchers initially maintained that the enzymes within this system degrade endocannabinoids because they activate the same receptors as the exogenous cannabinoid THC (Guindon & Hohmann, 2009), this early view was shown to be inaccurate (Watson et al., 2008). The ECS is found in the brain and other parts of the body. ECS has a pivotal function in many aspects of neurological development, including neural specification, neurogenesis, neural maturing, neuronal relocation, axonal augmentation, glia development, and arranging inhibitory GABAergic interneurons and excitatory glutamatergic neurons (De Petrocellis & Di Marzo, 2009). Thus, when this system becomes distressed, it is susceptible to many illnesses, including schizophrenia (Svíženská et al., 2008).

When the ECS becomes distressed by superfluous stimulation in a rapidly changing brain, such as adolescence and young adult cannabis use, it may have significant consequences for one's psychological functioning. This distress would be particularly problematic for a developing brain with a previous altered neurodevelopmental process—that is, "the diathesis" for schizophrenia or other psychotic illness. Thus, by disrupting the ECS and disturbing the neurodevelopmental processes, exposure to exogenous cannabinoids during the critical period may confer increased risk for the development of psychosis and schizophrenia. If a diathesis is present, this critical period may lead to the emergence of schizophrenia.

Age of Onset of Cannabis Use and the Emergence of Schizophrenia

Multiple studies suggest that adolescence is a critical period of increased vulnerability to the deleterious effects of frequent cannabis use (Gorey et al., 2019). The earlier the onset, the more severe the impairment of cognitive domains such as learning, decision-making, memory, and attention (Fontes et al., 2011; Gruber et al., 2012). It is also essential to consider that studies examining the association of age of onset of cannabis use and schizophrenia may have numerous confounding factors (Lisdahl et al., 2013). For example, a longitudinal study of the association of adolescent cannabis use, academic performance, and mental health among 1037 participants followed from childhood to adulthood. Participants were assessed at various periods of development, both before the age of onset, between ages 7-13, and at age 38. Researchers discovered that those between 7 and 13 years of age who self-reported frequent cannabis exposure or those who received a diagnosis of a cannabis-use disorder before age 18 displayed more neuropsychological deficits than those with a cannabis-use disorder or regular use limited to adulthood (Meier et al., 2012).

Furthermore, adolescents who use cannabis more than once daily may have irregularities that persist several years after abstinence, and results are reproducible in adult samples (Pope et al., 2003). Pope et al. (2003), elucidated the probability of premorbid aberrations that account for the successive decay in neuromasturational progression. The continuous abstinence from THC was not enough to recover cognitive abilities when heavy cannabis use is present in adolescence (Pope et al., 2003). Nevertheless, many have argued that the correlation between early-onset cannabis use, and cognitive deficits reported by Meier et al., (2012) may have been confounded by other factors such as socioeconomic status (Rogeberg, 2013) and personality (Daly, 2013). This possible confounding calls into question the causal nature of the cannabis-neurological relationship.

Others have argued that cannabis exposure is linked to schizophrenia in that it may commence during the premorbid phase of schizophrenia (D'Souza et al., 2005) and represent a form of self-medication while "feeling off" during this premorbid phase. According to D'Souza et al. (2005), individuals experiencing premorbid schizophrenia may use cannabis to alleviate symptoms. Although cannabis has been reported to exacerbate schizophrenia symptoms, some patients have said that they use it to "self-medicate" negative symptoms of schizophrenia, including depression, boredom, feelings of social inadequacy, as well as to address medication side-effects and fulfill a desire to experience positive affect and relaxation (Goswami et al., 2004). Of note, this evidence of cannabis use as self-medication derives from anecdotal self-reports, which may be subject to denial, rationalization, and other cognitive distortions characteristic of substance use disorder (Hall & Degenhardt, 2008). Also, many cannabis users in the premorbid phase of schizophrenia are polydrug users (Peters et al., 2010), and the ameliorating effects may not be attributable to cannabis solely. Epidemiological studies on cannabis use in the premorbid phase-contrast significantly with self-reports. Self-reports include cannabis use to reduce anxiety and "chill out." Thus, epidemiological studies on contrasting self-reports versus psychotic features may be necessary for further research to differentiate the immediate benefits of cannabis versus subsequent deleterious effects.

Earlier age of onset of cannabis use has also been positively correlated with more significant cognitive deficits in schizophrenia even with a short duration of use (Solowij et al., 2011). In a study assessing the consequences of early-onset cannabis use on learning and memory, Solowij et al. (2002), discovered that adolescents exposed to cannabis for 2.4 years on average displayed complex deficits in various cognitive domains than cross-referenced groups the nonsubstance-using control group of adolescents. The findings show that the extent and severity of cognitive deficits among adolescent cannabis users are comparable to that of adult users (Solowij et al., 2002). However, these effects materialized after fewer than three years of cannabis use throughout adolescence. Other research demonstrates that the earlier the age of onset of cannabis use, the higher the association with compromised functioning, even when magnitude and occurrence of use are controlled (Gruber et al., 2014). This evidence suggests that early onset of use may have a deleterious effect on cognitive ability irrespective of the magnitude of exposure (Solowij et al., 2011).

The adult literature has discussed factors that confound the association of cannabis use with cognitive deficits and schizophrenia. These include preexisting susceptibility to schizophrenia, frequency of use, and age of schizophrenia onset—all of which are also important to consider for adolescents. For example, in a longitudinal study by Caspi et al.

(2005), discovered that an existing diathesis influenced the impact of cannabis exposure on mental illness. Only those with a concomitant, recessive variation of catechol-O-methyltransferase (COMT) showed an increased risk of schizophrenia (Caspi et al., 2005). Environmental confounding factors include childhood trauma and growing up in a rural neighborhood (Houston et al., 2008; Harley et al., 2010; Kuepper et al., 2011). Indeed, a recent study examined the associations between child abuse, COMT genotypes, and psychosis, and variability in the COMT gene only affected psychosis in individuals who reported abuse during childhood (Alemany et al., 2014).

Evidence also indicated that cannabis exposure may contribute adversely to neurodevelopment (Sundram, 2006). Structural imaging findings, for instance, have demonstrated aberrations among adolescent users (Jacobus & Tapert, 2014). These effects are consistent with previous results that indicate smaller brain and cortical gray matter volumes, decreased prefrontal and insular cortical thickness, smaller right medial OFC volumes, smaller hippocampal volumes, greater left than right hippocampal symmetry, larger right amygdala volume in females, and larger amygdala in males (Wilson et al., 2000; Lopez-Larson et al., 2011; Churchwell et al., 2010; Ashtari et al., 2011; McQueeney et al., 2011). In addition, the finding that heavy and frequent cannabis use is positively correlated with a more prominent aberration in prefrontal regions of the brain suggests that this region of the brain may be particularly susceptible to the effects of cannabis use. Conversely, a smaller hippocampal mass has been positively correlated with heavier cannabis use—a finding does not differ based on the age of onset. This finding indicates that the duration and intensity of exposure rather than the period at the onset of cannabis use may be more aptly associated with schizophrenia (Lorenzetti et al., 2016). From this perspective, the decreased prefrontal volumes among heavy and frequent users could be attributed to variables that predate their cannabis use—that is, a preexisting diathesis (Cheetham et al., 2012). However, the study found no decrease in hippocampal volumes among adolescents who used cannabis. This finding is consistent with others showing that organizational differences in these brain regions are likely associated with frequent, heavy cannabis exposure (Squeglia et al., 2009).

During the critical period of adolescence, the brain is particularly susceptible to psychopharmacological insults. One study showed aberrations in the white matter among the heaviest users; however, the validity of the findings may have been compromised by confounding factors involving other substances (Baker et al., 2013). Yucel et al. (2010), discovered among a group of 11 adolescent cannabis users, 11 adolescent inhalant users, and 8 adolescent controls, there was a significant reduction in fractional anisotropy in the fasciculus

region adjacent to the right hippocampal area in cannabis exposed adolescents compared to controls. In a similar study by Ashtari et al. (2009), researchers recruited 14 young males with a history of cannabis and alcohol use who were residents of a substance abuse treatment facility. This study presented evidence of a reduction in fractional anisotropy in addition to increased radial diffusivity and increased trace values in frontotemporal regions in comparison to controls (Ashtari et al., 2009). Ashtari et al. (2009), suggested that these findings point to a disruption in the myelination process, but they also identify alcohol abuse as a confounding variable that was not controlled. Thus, these findings could indicate a synergistic effect of both cannabis and alcohol. Also, contemporary research has suggested an aberration in the white matter of the brains of adolescents who partake in cannabis use while abusing alcohol simultaneously and among adolescents without concomitant alcohol use (Jacobus et al., 2009; Bava et al., 2013; Jacobus et al., 2013). Polydrug use can have latent effects when coupled with *Cannabis sativa*.

Latent Effects of Cannabis Use

Chronic use of cannabis has been consistently shown to impair numerous cognitive processes in both adolescents and adults, such as working memory, attention, learning, and executive functions (Ranganathan & D'souza, 2006; Solowij & Pesa, 2012). Some of the most salient consequences have been found in information coding, verbal and nonverbal communication retrieval, and consolidation (Wilson et al., 1994; D'Souza et al., 2004; Ilan et al., 2004; Lane et al., 2005). In these studies, impairment has also been consistently noted in focused, selective, and divided attention. Most significantly, cannabis exposure during adolescence has been shown to produce schizophrenia-like cognitive impairments in otherwise healthy individuals (D'Souza et al., 2004; Morrison et al., 2009). However, it is essential to clarify that a systematic review of studies examining the effects of acute administration of THC yielded variable results across a wide range of domains (Zuurman et al., 2009). Researchers determined that while memory and attention effects showed many dose-response associations, results were not reproducible with differing neurocognitive tests. Furthermore, only heart rate served as a measurable and consistent biomarker of cannabis intoxication (Lubman et al., 2015).

Former users who commenced use during adolescence demonstrate lower cerebral blood flow in prefrontal, orbitofrontal cortices, cerebellum, striatum, temporal lobes, and globally (Lundqvist et al., 2001; Sevy et al., 2008). Also, in the study, a positive correlation of schizophrenia-like symptoms and cannabis exposure was observed in former users who began use during adolescence with no history of schizophrenia or a schizophreniform disorder

(Lundqvist et al., 2001). This study included participants who began cannabis use in adolescence but abstained during adulthood. This evidence suggests that a diathesis may not require psychotic symptoms amongst heavy cannabis users (Yücel et al., 2008). Although this evidence still does not establish a causal relationship between heavy cannabis use and psychosis, it suggests that a correlational relationship should not be discounted.

Although evidence of structural aberrations related to cannabis use is not enough to provide evidence of a causal association between cannabis use and psychosis or schizophrenia, this evidence exists among adolescents and adults who have used cannabis (Lorenzetti et al., 2016). Although findings for brain regions were varied, evidence supports those reductions in parahippocampal and hippocampal volumes were associated with greater lifetime cannabis exposure (Yücel et al., 2008). In a recent study, hippocampal shape alterations were examined in cannabis users with and without schizophrenia. Researchers found that aberrations in morphology across the hippocampus were associated with heavy cannabis use and symptoms of psychosis (Solowij et al., 2013). These findings point towards a positive correlation between greater cannabis use and morphological alterations in parahippocampal and hippocampal regions; however, as stated previously, the paucity of this research and varied findings in current studies warrant further investigation to clarify the association between cannabis use and parahippocampal and hippocampal aberrations in users.

In addition to Magnetic Resonance Imaging (MRI) studies, researchers have used Diffusion Tensor Imaging (DTI) to evaluate white matter in adult cannabis users. This process involves mapping water molecule diffusion, white matter microstructure, and anatomical connectivity. Due to other substances besides cannabis, it has been challenging to isolate THC; thus, these studies have been limited. However, the few studies that have been conducted support the notion that heavy cannabis use is associated with abnormalities in the white matter within the frontal, brain regions, hippocampal regions, and the corpus callosum (Gruber & Yurgelun-Todd, 2005; Gruber et al., 2012). In addition, many of these studies have also supported the notion that poor white matter integrity positively correlates with early-onset cannabis use (Gruber et al., 2012; Zalesky et al., 2012; Gruber et al., 2014). For example, Zalesky et al. (2012), reported anomalies in axonal fiber connectivity in the right fimbria of the hippocampus, splenium of the corpus callosum, and commissural fibers. There was also evidence of impaired connectivity in the fimbria and commissural fibers that are positively correlated with the age of onset of heavy cannabis use (Zalesky et al., 2012)—a finding that persisted after controlling for duration of consistent use and that supports the notion that heavy cannabis use during adolescence may be more harmful than adult exposure. Furthermore, it

supports studies in adults showing that the earlier that age of onset of cannabis use, the greater the cognitive impairment and more pronounced morphological aberrations (Jacobus et al., 2009; Lorenzetti et al., 2020). This comparison of heavy cannabis use effects in adults and adolescents extends to the Intelligence Quotient (IQ).

Meier et al. (2012), conducted a longitudinal study utilizing the Wechsler Intelligence Scale for Children-Revised, or Adults-IV administered to seven, nine, eleven, thirteen, and eighteen-year-olds. Those tested determined to be dependent on cannabis before the age of eighteen had a 0.55 standard deviation reduction in IQ compared to those defined as dependent after eighteen years of age (Meier et al., 2012). In addition, adolescents, seemingly, are more vulnerable to intellectual deficits succeeding cannabis use than adults (Gorey et al., 2019).

Conclusion

In this literature review, the impact of cannabis use on the adolescent brain and the associations of cannabis use with psychosis and schizophrenia during adolescence were considered. Indeed, many harmful effects of frequent cannabis use seem to predicate whether cannabis use commences during adolescence. However, it is critical to consider the inimitable neurobiological aberrations and potential confounds occurring during this crucial period. The outcomes of cannabis use on the endocannabinoid system have been contextualized regarding neuromaturation occurring throughout adolescence. A summary of the literature on the effects of cannabis use among those with and without a predisposition to schizophrenia has also been presented. The influence of cannabis use was considered on the developing endocannabinoid system, explicitly highlighting the results of studies examining if heavy and frequent cannabis exposure is positively correlated with significant morphological aberrations in white matter neuromaturation development. This review will contribute to the literature and understanding of the susceptibility of this population and elucidate the contradictions and ambiguities in the research on cannabis exposure and developmental psychiatry and psychology. Implications for further research include the likely instances of polydrug use. In many situations, cannabis users abuse psychedelics, alcohol, and narcotics in conjunction with cannabis. Polydrug use may cause various mental health pathologies and warrants further investigation.

References

Abush, H., Ghose, S., Van Enkevort, E. A., Clementz, B. A., Pearlson, G. D., Sweeney, J. A., & Ivleva, E. I. (2018). Associations between adolescent cannabis use and brain structure in psychosis. *Psychiatry Research: Neuroimaging*, 276, 53-64.

- Adams, I. B., & Martin, B. R. (1996). Cannabis: Pharmacology and toxicology in animals and humans. *Addiction*, 91(11), 1585-1614.
- Aleman, S., Moya, J., Ibáñez, M.I., Villa, H., Mezquita, L., Ortet, G., Gastó, C., Fañanás, L. and Arias, B., 2016. Childhood trauma and the rs1360780 SNP of FKBP5 gene in psychosis: a replication in two general population samples. *Psychological medicine*, 46(1), pp.221-223.
- American Psychiatric Association Division of Research. (2013). Highlights of changes from dsm-iv to dsm-5: Somatic symptom and related disorders. *Focus*, 11(4), 525-527.
- Ashtari, M., Cervellione, K., Cottone, J., Ardekani, B. A., & Kumra, S. (2009). Diffusion abnormalities in adolescents and young adults with a history of heavy cannabis use. *Journal of psychiatric research*, 43(3), 189-204.
- Ashtari, M., Avants, B., Cyckowski, L., Cervellione, K.L., Roofeh, D., Cook, P., Gee, J., Sevy, S. and Kumra, S., 2011. Medial temporal structures and memory functions in adolescents with heavy cannabis use. *Journal of psychiatric research*, 45(8),1055-1066.
- Baker, S. T., Yücel, M., Fornito, A., Allen, N. B., & Lubman, D. I. (2013). A systematic review of diffusion weighted MRI studies of white matter microstructure in adolescent substance users. *Neuroscience & Biobehavioral Reviews*, 37(8), 1713-1723.
- Bergamaschi, M.M., Queiroz, R.H.C., Chagas, M.H.N., De Oliveira, D.C.G., De Martinis, B.S., Kapczinski, F., Quevedo, J., Roesler, R., Schröder, N., Nardi, A.E. and Martín-Santos, R., 2011. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. *Neuropsychopharmacology*, 36(6),1219-1226.
- Bossong, M. G., & Niesink, R. J. (2010). Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. *Prog Neurobiol*, 92(3), 370–385.
- Brisch, R., Saniotis, A., Wolf, R., Bielau, H., Bernstein, H.G., Steiner, J., Bogerts, B., Braun, K., Jankowski, Z., Kumaratilake, J. and Henneberg, M., 2014. The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue. *Frontiers in psychiatry*, 5, p.47.
- Caballero, A., & Tseng, K. Y. (2012). Association of cannabis use during adolescence, prefrontal CB1 receptor signaling, and schizophrenia. *Front Pharmacol*, 3, 101.

- Caspi, A., Moffitt, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A. and Poulton, R., 2005. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biological psychiatry*, 57(10),1117-1127.
- Ceccarini, J., De Hert, M., Van Winkel, R., Peuskens, J., Bormans, G., Kranaster, L., Enning, F., Koethe, D., Leweke, F.M. and Van Laere, K. (2013). Increased ventral striatal CB1 receptor binding is related to negative symptoms in drug-free patients with schizophrenia. *Neuroimage*, 79, 304-312.
- Cheetham, A., Allen, N. B., Whittle, S., Simmons, J. G., Yücel, M., & Lubman, D. I. (2012). Orbitofrontal volumes in early adolescence predict initiation of cannabis use: a 4-year longitudinal and prospective study. *Biological psychiatry*, 71(8), 684-692.
- Churchwell, J. C., Lopez-Larson, M., & Yurgelun-Todd, D. A. (2010). Altered frontal cortical volume and decision making in adolescent cannabis users. *Frontiers in Psychology*, 1, 225.
- Daly, M. (2013). Personality may explain the association between cannabis use and neuropsychological impairment. *Proceedings of the National Academy of Sciences*, 110(11), E979-E979.
- De Petrocellis, L., & Di Marzo, V. (2009). An introduction to the endocannabinoid system: from the early to the latest concepts. *Best practice & research Clinical endocrinology & metabolism*, 23(1), 1-15.
- Díaz-Alonso, J., Guzmán, M., & Galve-Roperh, I. (2012). Endocannabinoids via CB1 receptors act as neurogenic niche cues during cortical development. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 367(1607), 3229-3241.
- Downer, E. J., & Campbell, V. A. (2010). Phytocannabinoids, CNS cells, and development: A dead issue? *Drug Alcohol Rev*, 29(1), 91–98.
- D'Souza, D.C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y.T., Braley, G., Gueorguieva, R. and Krystal, J.H., 2004. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*, 29(8), pp.1558-1572.

- D'Souza, D.C., Abi-Saab, W.M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G., Gueorguieva, R., Cooper, T.B. and Krystal, J.H., 2005. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biological psychiatry*, 57(6), pp.594-608.
- Eggan, S. M., Stoyak, S. R., Verrico, C. D., & Lewis, D. A. (2010). Cannabinoid CB1 receptor immunoreactivity in the prefrontal cortex: comparison of schizophrenia and major depressive disorder. *Neuropsychopharmacology*, 35(10), 2060-2071.
- Ferretjans, R., Moreira, F. A., Teixeira, A. L., & Salgado, J. V. (2012). The endocannabinoid system and its role in schizophrenia: a systematic review of the literature. *Revista brasileira de psiquiatria*, 34, 163-193.
- Freund, T. F., Katona, I., & Piomelli, D. (2003). Role of endogenous cannabinoids in synaptic signaling. *Physiological reviews*.
- Fride, E. (2008). Multiple roles for the endocannabinoid system during the earliest stages of life: Pre- and postnatal development. *J Neuroendocrinol*, 20(s1), 75–81.
- Fontes, M.A., Bolla, K.I., Cunha, P.J., Almeida, P.P., Jungerman, F., Laranjeira, R.R., Bressan, R.A. and Lacerda, A.L. (2011). Cannabis use before age 15 and subsequent executive functioning. *The British Journal of Psychiatry*, 198(6), pp.442-447.
- Galve-Roperh, I., Aguado, T., Palazuelos, J., & Guzmán, M. (2007). The endocannabinoid system and neurogenesis in health and disease. *Neuroscientist*, 13(2), 109–114.
- Galve-Roperh, I., Palazuelos, J., Aguado, T., & Guzmán, M. (2009). The endocannabinoid system and the regulation of neural development: Potential implications in psychiatric disorders. *Eur Arch Psychiatry Clin Neurosci*, 259(7), 371–382.
- Galve-Roperh, I. (2012). Cannabis, endocannabinoids, and neurodevelopment. *Marijuana and Madness*, 66.
- Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C. and Rapoport, J.L., 1999. Brain development during childhood and adolescence: a longitudinal MRI study. *Nature neuroscience*, 2(10), pp.861-863.
- Giedd, J. N., Lalonde, F. M., Celano, M. J., White, S. L., Wallace, G. L., Lee, N. R., & Lenroot, R. K. (2009). Anatomical brain magnetic resonance imaging of typically developing children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, 48(5), 465.

- Guindon, J., & Hohmann, A. G. (2009). The endocannabinoid system and pain. *CNS & Neurological Disorders-Drug Targets*, 8(6), 403-421.
- Gruber, S. A., & Yurgelun-Todd, D. A. (2005). Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation. *Cognitive Brain Research*, 23(1), 107-118.
- Gruber, S. A., Sagar, K. A., Dahlgren, M. K., Racine, M., & Lukas, S. E. (2012). " Age of onset of marijuana use and executive function": Correction to Gruber et al. (2011).
- Gruber, S. A., Dahlgren, M. K., Sagar, K. A., Gönenç, A., & Lukas, S. E. (2014). Worth the wait: Effects of age of onset of marijuana use on white matter and impulsivity. *Psychopharmacology*, 231(8), 1455-1465.
- Gorey, C., Kuhns, L., Smaragdi, E., Kroon, E., & Cousijn, J. (2019). Age-related differences in the impact of cannabis use on the brain and cognition: a systematic review. *European archives of psychiatry and clinical neuroscience*, 269(1), 37-58.
- Goswami, S., Mattoo, S. K., Basu, D., & Singh, G. (2004). Substance-abusing schizophrenics: do they self-medicate?. *American Journal on Addictions*, 13(2), 139-150.
- Hall, W., & Degenhardt, L. (2008). Cannabis use and the risk of developing a psychotic disorder. *World Psychiatry*, 7(2), 68.
- Harkany, T., Keimpema, E., Barabás, K., & Mulder, J. (2008). Endocannabinoid function controlling neuronal specification during brain development. *Mol Cell Endocrinol*, 286(1), S84–S90.
- Harley, M., Kelleher, I., Clarke, M., Lynch, F., Arseneault, L., Connor, D., Fitzpatrick, C. and Cannon, M., 2010. Cannabis use and childhood trauma interact additively to increase the risk of psychotic symptoms in adolescence. *Psychological medicine*, 40(10), pp.1627-1634.
- Harvey, M. A., Sellman, J. D., Porter, R. J., & Frampton, C. M. (2007). The relationship between non-acute adolescent cannabis use and cognition. *Drug and Alcohol Review*, 26(3), 309-319.
- Houston, J. E., Murphy, J., Adamson, G., Stringer, M., & Shevlin, M. (2008). Childhood sexual abuse, early cannabis use, and psychosis: testing an interaction model based on the National Comorbidity Survey. *Schizophrenia bulletin*, 34(3), 580-585.

- Ilan, A. B., Smith, M. E., & Gevins, A. (2004). Effects of marijuana on neurophysiological signals of working and episodic memory. *Psychopharmacology*, 176(2), 214-222.
- Jacobus, J., Bava, S., Cohen-Zion, M., Mahmood, O., & Tapert, S. F. (2009). Functional consequences of marijuana use in adolescents. *Pharmacology Biochemistry and Behavior*, 92(4), 559-565.
- Jacobus, J., & Tapert, S. F. (2013). Neurotoxic effects of alcohol in adolescence. *Annual review of clinical psychology*, 9, 703-721.
- Jacobus, J., Squeglia, L. M., Bava, S., & Tapert, S. F. (2013). White matter characterization of adolescent binge drinking with and without co-occurring marijuana use: a 3-year investigation. *Psychiatry Research: Neuroimaging*, 214(3), 374-381.
- Jacobus, J., & F Tapert, S. (2014). Effects of cannabis on the adolescent brain. *Current Pharmaceutical Design*, 20(13), 2186-2193.
- Kuepper, R., van Os, J., Lieb, R., Wittchen, H. U., Höfler, M., & Henquet, C. (2011). Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *Bmj*, 342.
- Lane, S. D., Cherek, D. R., Tcheremissine, O. V., Lieving, L. M., & Pietras, C. J. (2005). Acute marijuana effects on human risk taking. *Neuropsychopharmacology*, 30(4), 800-809.
- Laruelle, M., Kegeles, L. S., & Abi-Dargham, A. (2003). Glutamate, dopamine, and schizophrenia. *Ann NY Acad Sci*, 1003, 138-158.
- Lisdahl, K. M., Gilbert, E. R., Wright, N. E., & Shollenbarger, S. (2013). Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. *Frontiers in psychiatry*, 4, 53.
- Lopez-Larson, M. P., Bogorodzki, P., Rogowska, J., McGlade, E., King, J. B., Terry, J., & Yurgelun-Todd, D. (2011). Altered prefrontal and insular cortical thickness in adolescent marijuana users. *Behavioural brain research*, 220(1), 164-172.
- Lorenzetti, V., Alonso-Lana, S., J Youssef, G., Verdejo-Garcia, A., Suo, C., Cousijn, J., Takagi, M., Yucel, M. and Solowij, N., 2016. Adolescent cannabis use: What is the evidence for functional brain alteration?. *Current pharmaceutical design*, 22(42), 6353-6365.
- Lorenzetti, V., Hoch, E., & Hall, W. (2020). Adolescent cannabis use, cognition, brain health and educational outcomes: a review of the evidence. *European Neuropsychopharmacology*, 36, 169-180.

- Lubman, D. I., Cheetham, A., & Yücel, M. (2015). Cannabis and adolescent brain development. *Pharmacology & therapeutics*, 148, 1-16.
- Lundqvist, T., Jönsson, S., & Warkentin, S. (2001). Frontal lobe dysfunction in long-term cannabis users. *Neurotoxicology and teratology*, 23(5), 437-443.
- Mackie, K. (2008). Cannabinoid receptors: where they are and what they do. *Journal of neuroendocrinology*, 20, 10-14.
- Malone, D. T., Hill, M. N., & Rubino, T. (2010). Adolescent cannabis use and psychosis: Epidemiology and neurodevelopmental models. *Br J Pharmacol*, 160(3), 511–522.
- Marsicano, G., Goodenough, S., Monory, K., Hermann, H., Eder, M., Cannich, A., Azad, S.C., Cascio, M.G., Gutiérrez, S.O., Van der Stelt, M. and López-Rodríguez, M.L., 2003. CB1 cannabinoid receptors and on-demand defense against excitotoxicity. *Science*, 302(5642), 84-88.
- Marsicano, G., & Lafenêtre, P. (2009). Roles of the endocannabinoid system in learning and memory. *Behavioral Neurobiology of the Endocannabinoid System*, 201–230.
- McQueeney, T., Padula, C. B., Price, J., Medina, K. L., Logan, P., & Tapert, S. F. (2011). Gender effects on amygdala morphometry in adolescent marijuana users. *Behavioural brain research*, 224(1), 128-134.
- Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S., McDonald, K., Ward, A., Poulton, R., & Moffitt, T. E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences of the United States of America*, 109(40), E2657–E2664. <https://doi.org/10.1073/pnas.1206820109>
- Morrison, P.D., Zois, V., McKeown, D.A., Lee, T.D., Holt, D.W., Powell, J.F., Kapur, S. and Murray, R.M., 2009. The acute effects of synthetic intravenous Δ 9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. *Psychological medicine*, 39(10), 1607-1616.
- Newell, K. A., Deng, C., & Huang, X. F. (2006). Increased cannabinoid receptor density in the posterior cingulate cortex in schizophrenia. *Experimental Brain Research*, 172(4), 556-560.

- Oleson, E. B., & Cheer, J. F. (2012). A brain on cannabinoids: The role of dopamine release in reward seeking. *Cold Spring Harbor Perspectives in Medicine*, 2(8), a012229.
<https://doi.org/10.1101/cshperspect.a012229>
- Parolaro, D., Realini, N., Vigano, D., Guidali, C., & Rubino, T. (2010). The endocannabinoid system and psychiatric disorders. *Experimental neurology*, 224(1), 3-14.
- Paus, T. (2005). Mapping brain maturation and cognitive development during adolescence. *Trends in cognitive sciences*, 9(2), 60-68.
- Peters, B. D., Blaas, J., & de Haan, L. (2010). Diffusion tensor imaging in the early phase of schizophrenia: What have we learned? *Journal of Psychiatric Research*, 44(15), 993-1004.
- Pope Jr, H. G., Gruber, A. J., Hudson, J. I., Cohane, G., Huestis, M. A., & Yurgelun-Todd, D. (2003). Early-onset cannabis use and cognitive deficits: what is the nature of the association?. *Drug and alcohol dependence*, 69(3), 303-310.
- Quickfall, J., & Crockford, D. (2006). Brain neuroimaging in cannabis use: a review. *The Journal of neuropsychiatry and clinical neurosciences*, 18(3), 318-332.
- Ranganathan, M., & D'Souza, D. C. (2006). The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology*, 188(4), 425-444.
- Rogeberg, O. (2013). Correlations between cannabis use and IQ change in the Dunedin cohort are consistent with confounding from socioeconomic status. *Proceedings of the National Academy of Sciences*, 110(11), 4251-4254.
- Sevy, S., Smith, G.S., Ma, Y., Dhawan, V., Chaly, T., Kingsley, P.B., Kumra, S., Abdelmessih, S. and Eidelberg, D., 2008. Cerebral glucose metabolism and D2/D3 receptor availability in young adults with cannabis dependence measured with positron emission tomography. *Psychopharmacology*, 197(4), 549-556.
- Steinberg, L. (2005). Cognitive and affective development in adolescence. *Trends in cognitive sciences*, 9(2), 69-74.
- Steinberg, L. (2007). Risk-taking in adolescence: New perspectives from brain and behavioral science. *Current Directions in Psychological Science*, 16(2), 55-59.
- Sullivan, J. M. (2000). Cellular and molecular mechanisms underlying learning and memory impairments produced by cannabinoids. *Learning & Memory*, 7(3), 132-139.

- Sundram, S. (2006). Cannabis and neurodevelopment: implications for psychiatric disorders. *Human Psychopharmacology: Clinical and Experimental*, 21(4), 245-254.
- Solowij, N., Michie, P. T., & Fox, A. M. (1995). Differential impairments of selective attention due to frequency and duration of cannabis use. *Biological Psychiatry*, 37(10), 731-739.
- Solowij, N., & Grenyer, B. F. (2002). Are the adverse consequences of cannabis use age-dependent?. *Addiction*, 97(9), 1083-1086.
- Solowij, N., Stephens, R.S., Roffman, R.A., Babor, T., Kadden, R., Miller, M., Christiansen, K., McRee, B., Vendetti, J. and Marijuana Treatment Project Research Group. (2002). Cognitive functioning of long-term heavy cannabis users seeking treatment. *Jama*, 287(9),123-1131.
- Solowij, N., Yücel, M., Respondek, C., Whittle, S., Lindsay, E., Pantelis, C., & Lubman, D. I. (2011). Cerebellar white-matter changes in cannabis users with and without schizophrenia. *Psychological medicine*, 41(11), 2349-2359.
- Solowij, N., & Pesa, N. (2012). Cannabis and cognition: short and long-term effects. *Marijuana and madness*, 2, 91-102.
- Solowij, N., Walterfang, M., Lubman, D.I., Whittle, S., Lorenzetti, V., Styner, M., Velakoulis, D., Pantelis, C. and Yücel, M. (2013). Alteration to hippocampal shape in cannabis users with and without schizophrenia. *Schizophrenia research*, 143(1), pp.179-184.
- Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience & biobehavioral reviews*, 24(4), 417-463.
- Squeglia, L. M., Jacobus, J., & Tapert, S. F. (2009). The influence of substance use on adolescent brain development. *Clinical EEG and neuroscience*, 40(1), 31-38.
- Svíženská, I., Dubový, P., & Šulcová, A. (2008). Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures—a short review. *Pharmacology Biochemistry and Behavior*, 90(4), 501-511.
- Watson, S., Chambers, D., Hobbs, C., Doherty, P., & Graham, A. (2008). The endocannabinoid receptor, CB1, is required for normal axonal growth and fasciculation. *Molecular and Cellular Neuroscience*, 38(1), 89-97.

- Wilson, W. H., Ellinwood, E. H., Mathew, R. J., & Johnson, K. (1994). Effects of marijuana on performance of a computerized cognitive-neuromotor test battery. *Psychiatry research*, 51(2), 115-125.
- Wilson, W., Mathew, R., Turkington, T., Hawk, T., Coleman, R. E., & Provenzale, J. (2000). Brain morphological changes and early marijuana use: a magnetic resonance and positron emission tomography study. *Journal of addictive diseases*, 19(1), 1-22.
- Wong, D.F., Kuwabara, H., Horti, A.G., Raymond, V., Brasic, J., Guevara, M., Ye, W., Dannals, R.F., Ravert, H.T., Nandi, A. and Rahmim, A. (2010). Quantification of cerebral cannabinoid receptors subtype 1 (CB1) in healthy subjects and schizophrenia by the novel PET radioligand [11C] OMAR. *Neuroimage*, 52(4),1505-1513.
- Yücel, M., Solowij, N., Respondek, C., Whittle, S., Fornito, A., Pantelis, C., & Lubman, D. I. (2008). Regional brain abnormalities associated with long-term heavy cannabis use. *Archives of general psychiatry*, 65(6), 694-701.
- Zalesky, A., Solowij, N., Yücel, M., Lubman, D.I., Takagi, M., Harding, I.H., Lorenzetti, V., Wang, R., Searle, K., Pantelis, C. and Seal, M. (2012). Effect of long-term cannabis use on axonal fibre connectivity. *Brain*, 135(7), 2245-2255.
- Zavitsanou, K., Garrick, T., & Huang, X. F. (2004). Selective antagonist [3H] SR141716A binding to cannabinoid CB1 receptors is increased in the anterior cingulate cortex in schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 28(2), 355-360.
- Zuardi, A. W., Shirakawa, I., Finkelfarb, E., & Karniol, I. G. (1982). Action of cannabidiol on the anxiety and other effects produced by Δ^9 -THC in normal subjects. *Psychopharmacology*, 76(3), 245-250.
- Zuardi, A. W., Cosme, R. A., Graeff, F. G., & Guimarães, F. S. (1993). Effects of ipsapirone and cannabidiol on human experimental anxiety. *Journal of psychopharmacology*, 7(1_suppl), 82-88.
- Zuardi, A. W., Crippa, J. A. D. S., Hallak, J. E. C., Moreira, F. A., & Guimaraes, F. S. (2006). Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Brazilian journal of medical and biological research*, 39, 421-429.

Zuurman, L., Ippel, A. E., Moin, E., & Van Gerven, J. M. (2009). Biomarkers for the effects of cannabis and THC in healthy volunteers. *British journal of clinical pharmacology*, 67(1), 5-21.