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Effects of Chronic Cannabis Use on Adolescents

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Abstract

This literature review examines the relationship of chronic cannabis use during adolescence to psychological and morphological abnormalities into adulthood. As states continue to decriminalize or legalize cannabis consumption for recreational purposes, concerns about the potential negative effects of cannabis consumption on neurological development during adolescence may be ignored. This review examined 44 journal articles and government reports published between 1997 and 2021. The conclusions drawn from the literature review indicate that over a 19-year time span, cannabis potency has increased from ~ 4% to ~12%. Secondly, the chronic exposure to exogenous cannabinoids during this time can result in a variety of negative outcomes due to the dysregulation of the endocannabinoid system, one of the systems responsible for fostering brain development. Finally, the literature suggests that specific domains of worry are those of memory, attention, cognition, and emotional regulation as regions responsible for these functions are highly susceptible to alterations due to their elevated levels of CB1 receptors. Inconsistencies in terminology and parameters used to define chronic use are also addressed across all literature referenced in this review.

Keywords: cannabis, marijuana, chronic use, THC, cannabinoids adolescent, development, brain, maturation, potency, dysregulation

Effects of Chronic Cannabis Use on Adolescents

For over four thousand years, there has been well-documented use of cannabis across the world (Aggarwal et al., 2009). Cannabinoids are chemical components present within the Cannabis plant (Kafil et al., 2018). The makeup of the endocannabinoid system consists of endocannabinoids which are endogenous ligands, as well as CB1 and CB2 receptors and associated enzymes (Kafil et al., 2018). Cannabis primarily consists of two main cannabinoids. *Cannabidiol* is becoming an increasingly mainstream treatment for a range of issues, including anxiety, sore muscles, and insomnia (Aggarwal et al., 2009). The other well-known cannabinoid is *tetrahydrocannabinol*, recognized as the chemical responsible for creating the "high" feeling when cannabis is used (Mechoulam & Parker, 2012). Although many societies have used cannabis for an extensive amount of time, there is still much to understand regarding how chronic cannabis use and high *tetrahydrocannabinol* potency interact with the body and its developmental processes (Wilson et al., 2019).

With more states legalizing adult consumption of cannabis on a recreational level, the perceived danger of cannabis is declining as it becomes normalized in society (Wilson et al., 2019; Gruber et al., 2014). This reduction in perceived danger is cause for concern, particularly in the domain of adolescent brain development and the psychological effects that result from chronic use of cannabis. The endocannabinoid system, present in all animal species except insects, plays a vital role in the regulation and development of immune responses, appetite, metabolism, memory, and brain activity/maturation (Mechoulam & Parker, 2012). This system interacts with the cannabinoids through the CB1 and CB2 G protein-coupled receptors (Mechoulam & Parker, 2012). Heavy focus should be placed on this topic because, during adolescence, the brain is in a transitional phase (Jacobus & Tapert, 2014).

During this phase, there is a reduction in the number of synapses in cortical and subcortical structures and changes at the neurotransmitter and receptor levels (Fontes et al., 2011). Synaptic pruning is a typical process that occurs throughout development, where synapses are deconstructed to allow for new connections to be made while myelination of useful connections is increased (Lubman et al., 2014). Both these processes may be negatively impacted through cannabis exposure during this critical window of development (Lubman et al., 2014). Peak gray matter volumes are reached between the ages of 12-14 years old, and following this, there is a rapid but regulated loss of grey matter. This regulation is due in part to the endocannabinoid system, which plays a key role in brain development until late adolescence (Jacobus et al., 2015).

These changes make adolescents particularly vulnerable to developing substance abuse disorders, significantly disrupting the reorganization and development of the brain (Jacobus et al., 2015). The chronic exposure to exogenous cannabinoids present in the drug has wide-ranging effects on adolescent neurodevelopment, including impaired healthy astrocyte function, prevention of the formation of new synapses, or decreased levels of dopamine resulting in apathy (Fontes, 2011; Shollenbarger, 2015). These wide-reaching effects have an impact on the mental and physical well-being of adolescents, whether it is a drop in academic performance and motivation or, more seriously, impairing daily function due to a loss in working memory capacity (Gonzalez, 2007). This literature review will focus on how chronic cannabis use during adolescence may result in morphological abnormalities across the developing brain and the psychological effects that are associated with chronic use.

Method

Articles for this literature review were collected from two databases, Psychinfo and Google Scholar, and the dates of the articles ranged between 1994 to 2021. However, articles from before 1994 were not included in the search criteria as THC concentrations saw little to no increase before this time, making any information from prior to 1994 irrelevant to the focus of this literature review. Research for this review began in the Spring of 2021 and ended in the Spring of 2023. Keywords (i.e., cannabis, marijuana, chronic use, THC, cannabinoids adolescent, development, brain, maturation, potency, dysregulation) were used to find articles appropriate for review.

During the preliminary level of review, the abstract was read along with the discussion to ascertain whether or not an article would be included in a more thorough review. Sixty-one articles and reports were retained for secondary review, involving a complete read-through. If the paper contained content pertinent to our research questions, it was retained for the final level of review. Forty-four peer-reviewed articles survived the secondary level of review and were retained for the final review, including 29 empirical research reports, 12 systematic reviews and meta-analyses, and three governmental reports.

Cannabis Use and Potency

While there are over 500 compounds and nearly 100 cannabinoids within cannabis, the potency of the drug is typically judged according to the level of tetrahydrocannabinol (ElSohly, 2016). Through a best-worst scaling experiment (Zhu et al., 2021), data were collected to examine what factors affect the choice of cannabis in dispensaries. The study revealed that, in general, the most important factors involved include "quality," "strain type," "price," "THC," and "pesticide" (Zhu et al., 2016). While the study did not examine adolescents, it included ages 21+, with 41.37% being 21-29, 30-44 making up 36.11%, and 22.52% were 45+ (Zhu et al., 2021).

While this age group is not the particular focus of this review, this becomes a salient and related aspect to consider when one considers the trajectory of brain development.

In an analysis of cannabis potency over two decades spanning from 1995-2014, results showed an average increase from ~ 4% to ~12% (ElSohly, 2016). It is also key to note that there are multiple forms of cannabis found on the illicit market (ElSohly, 2016). Marijuana is the common umbrella term for cannabis products, but it is simply the male or female plant grown for any use (ElSohly, 2016). *Sinsemilla*, meaning "seedless" in Spanish, is the female cannabis plant that has not been pollinated. The samples showed a strong declining trend in marijuana prevalence from 2002 through 2014, while sinsemilla prevalence indicated a steady increase (ElSohly, 2016). In accordance with increasing *tetrahydrocannabinol* levels and the previously mentioned trends, a possible explanation would be that because sinsemilla has a much higher level of potency, those growing the plants seek a stronger effect as they phase out marijuana in favor of sinsemilla. This is apparent when comparing *tetrahydrocannabinol* potency, as sinsemilla has more than twice the level of potency versus marijuana (ElSohly, 2016). Hash oil is collected by solvent extraction from the cannabis plant, where the solvents are then evaporated, leaving highly concentrated oil. There are other forms of cannabis less well known, such as thai sticks, kilobrick, hashish, and ditchweed (ElSohly, 2016).

Over a twenty-year period, cannabis samples were collected by law enforcement agents and submitted to eight Drug Enforcement Agency regional laboratories (ElSohly, 2016). Of the samples received and analyzed over the collection period, 26,145 samples were marijuana, 11,344 samples were sinsemilla, and 115 of the samples were ditchweed. Most samples fall under the plant material category, which consists of the dried flower from the plant, with hash oil

containing the highest tetrahydrocannabinol concentration, followed by hashish and then cannabis (ElSohly, 2016).

Short-term effects of increasing cannabis potency on adolescents have already been observed. In adolescents 15-17 years old, reported emergency department visits involving marijuana use saw a 53.6% increase in boys and a 42.9% increase in girls from 2005 to 2010. The Substance Abuse and Mental Health Services Administration announced steadily declining numbers of adolescent users from 2016-2018 (McCance-Katz, 2020). However, with continued legalization or decriminalization of cannabis across the United States, a 1.6% increase in usage from 2018 to 2019 was reported (McCance-Katz, 2020). In 2019, the administration announced a sharp increase in young adult use, increasing 0.9% (~200k) from 2018 (McCance-Katz, 2020). Prevalence of cannabis use disorder in adolescents saw a significant increase from 2018 to 2019, increasing 0.7% (~187k; McCance-Katz, 2020).

Annual marijuana use has increased over the past five years for college students reaching the highest levels seen in over thirty-five years (NIDA, 2021). Reported marijuana use shows a steady rise, with 44% of college students reporting use of marijuana during 2020 in comparison to 38% reporting use in 2015 (NIDA, 2021). Reported daily or near-daily use continues to rise in college students since 2015, with 8% reporting daily use in 2020 compared to 5% daily use in 2015 (NIDA, 2021). For young adults not in college, annual use remained at 43% in 2020, the same historically high level recorded in 2018 and 2019, with 13% reporting daily use, which has remained consistent with recent years (NIDA, 2021). Between 2017-2019 college-age adults who reported vaping marijuana (hash oil) within the last thirty days nearly tripled from 5% to 14% for college students and increased from 8% to 17% for young adults not in college (NIDA, 2021). In 2020 these numbers leveled off, with 12% of college students and 14% of non-college

young adults reporting vaping marijuana (NIDA, 2021). These increases in cannabis usage among adolescents and young adults are important because the brain is in a significant transition period where it is being "rewired" that is not completed until about 25 years of age (Arain et al., 2013).

Biological Interactions

The endocannabinoid system is responsible for a variety of processes within the human body. Throughout the lifespan, the system plays a key role in the development and maintenance of immune responses, metabolism, brain development, digestion, and more (Mechoulam & Parker, 2012; Wilson et al., 2019; Lubman et al., 2014). CB1 receptors are abundant within white matter during neural development and are seen diminishing during adulthood (Lubman et al., 2014; Gruber et al., 2014). Boer and colleagues (2010) investigated the expression and distribution of group I metabotropic glutamate receptors (mGluRs) during prenatal human cortical development. Results from the investigation found a differential expression pattern of mGluRs subtypes suggesting a role for these glutamate receptors in corticogenesis with a different contribution to human cortical developmental effects (Boer et al., 2010). The endocannabinoid-mediated control over glutamate transmission may be disrupted by chronic adolescent use, causing alterations in typical synaptic pruning and disruptions to prefrontal development (Lubman et al., 2014).

The greatest number of CB1 receptor binding sites in the human brain are in the forebrain areas, which are associated with higher cognitive functions; the forebrain, midbrain and hindbrain areas associated with movement control; and hindbrain areas associated with control of motor and sensory functions regarding the autonomic nervous system (Glass et al., 1997) Both the hippocampus and allocortical structures play a major part in sensory information coding and

memory storage; it has been hypothesized that that exogenous cannabinoids produce memory deficits through interaction with receptors in these structures depressing neural activity (Glass et al., 1997). Cannabinoid receptors are seen in greater numbers during youth, with receptor levels significantly higher in the prenatal and neonatal brain in comparison to the adult brain, particularly in the basal ganglia (Glass et al., 1997). While receptor quantity steadily diminishes over one's lifespan, CB1 receptors play dynamic roles within the brain, affecting neurotransmitter release and concentrations across neural systems as well as being thought to play a role in the genetic expression of neural development (Jacobus & Tapert, 2014).

Although gender, age of onset, and frequency of use may all be factors that contribute to varying effects of cannabis use, another important aspect that must be considered is a genetic perspective. Adolescents who use cannabis frequently may think their biology has little to do with how they process these exogenous cannabinoids; however, that is not the case. The gene COMT provides instruction to produce the protein catechol-O-methyltransferase, which appears to be an indication of a person's vulnerability to the negative effects of cannabis (Caspi et al., 2005, Schneider, 2008). Catechol-O-methyltransferase has been found to be involved in the metabolizing of dopamine released into synapses, and disturbances in these dopaminergic functions are involved in the pathogenesis of schizophrenia (Caspi et al., 2005; Schneider, 2008). The missense in focus is that of a G to A, resulting in the production of methionine rather than valine which causes slowed dopamine breakdown (Caspi et al., 2005). While this missense can predispose a person to negative outcomes such as the development of schizophrenia or other psychotic symptoms, there appears to be a buffer even if this missense occurs. Researchers found that the presence of two copies of the methionine acts in place of valine, as no adverse influence on individuals was recorded with their presence (Schneider, 2008). If the individual does not

have this missense present, early use can be a causal factor for further illicit drug use by inducing neurobiological alterations to reward-related systems in the developing brain (Schneider, 2008).

Examination of Approaches and Methodologies in the Literature

The wide variability in methodologies researchers have used to examine the effects of cannabis use during adolescence is an important issue. For example, defining early and late onset and distinguishing between light and heavy use are crucial issues in the investigations when the adolescent brain is most vulnerable to cannabis exposure. Similarly, the research design (i.e., cross-sectional or longitudinal) has long been shown to impact findings from developmental studies (Baltes, 1968). This portion will seek to differentiate studies based on their approach and methodology.

Distinguishing Groups

Making a distinction between groups of early versus late onset users and chronic versus acute/no use is a critical point in the interpretation of results. Studies specifying early onset were typically defined as use before mid-adolescence, with late-onset being after mid-adolescence. The specific parameters did vary by study, such as Fontes and others (2011) defining early onset as use before age fifteen and late onset as use after fifteen. The average lifetime estimations of use for the early onset group were 6,790 joints compared to the late onset group of 5,160 joints (Fontes et al., 2011). In a study completed by Jacobus and colleagues (2012) on altered cerebral blood flow and neurocognitive correlates in adolescent cannabis users, groups were not separated by age of onset as the investigation's purpose was simply to compare heavy users to nonusers. To qualify as heavy users, participants needed to have reported greater than two-hundred lifetime use days, with the control group recording less than four lifetime uses (Jacobus et al., 2012).

In an investigation of the impact of early onset use on functional brain correlates of working memory, Becker and colleagues (2010) included subjects that had reported minimum lifetime use of ten grams. Consistent with other investigators, Becker and colleagues (2010) distinguished between early and late-onset by setting a threshold at about mid-adolescence; the early onset group was defined by use prior to sixteen, with late-onset being characterized by first use after the age of sixteen (Becker et al., 2010; Jackson, 2016). The investigators also recorded a detailed history of participants' drug use, an aspect of their method that was not commonly found in the literature. The record of use included the following: (1) age of first use, (2) time since the last use in days, (3) average frequency of use measured by average days of use per month, (4) maximum days of use per month ever, (5) estimated cumulative lifetime dose, (6) average and (7) highest daily dose ever used, as well as (8) duration of regular use in months (Becker et al., 2010).

Assessment of Use

Within the literature, there are varying approaches taken to understand the implications of chronic cannabis use during adolescence. Although much of the existing literature involves cross-sectional studies, a few longitudinal studies have been done to better understand the issue across the lifespan (refer to Appendix for more details). However, there is a single cross-sectional twin study (Lynskey et al., 2004) and a longitudinal twin study (Jackson et al., 2016) which examines the genetic contribution of the impact of cannabis use on neurodevelopment. While it is crucial to differentiate between results based on methodology, it is important to consider these different approaches to the issue as each study may inform us of a new aspect previously unknown.

The methodology involved in these studies was found to be the most consistent compared to parameters for chronic use and the data collection technique. There is great fluctuation in how researchers define cannabis-using individuals, particularly heavy or chronic users, which can contribute to varying outcomes. The only form of consistency in this domain is apparent in researchers who elected to use the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) for cannabis dependence. The DSM-V was not used in these studies as it was not published at the time of the respective studies' conclusions. Of the studies reviewed, this only consisted of a very small percentage meaning that there is a massive disparity in how researchers define chronic use. Each other study elected to define chronic or heavy use in their own terms, whether it be quantitative, qualitative, or both. Jacobus and colleagues (2012) opted to define heavy use as anything greater than one hundred lifetime uses. Bava and others (2010) focused on cannabis use alongside alcohol use, as these substances are typically the most used among adolescents. Within this study, controls were limited to no more than five lifetime cannabis uses and fifty lifetime drinks, as well as no more than two lifetime uses of any other drug (Bava et al., 2010). Criteria for participants otherwise consisted of 180-1800 lifetime cannabis uses and 50-700 drinks (Bava et al., 2010).

While most researchers opted to define chronic use through "lifetime uses," others chose criteria that appeared unique to that study which may provide more reliable data as the definition of a single use is subjective and self-reported. For example, Jager and colleagues (2013) conducted a study in which participants were found to have consumed, on average, two joints per day, with some cases reaching eight to ten per day. Due to a lack of standardization, these parameters allow for potential confounds as there is no way of distinguishing between different strains consumed, which may contain varying levels of *tetrahydrocannabinol*. In addition, these

joints may have differing amounts of cannabis, which is another aspect to consider in the interpretation of results (Jager et al., 2013). Similarly, Ashtari and colleagues (2012) struggled to quantify the level of *tetrahydrocannabinol* and chose to report joints per day with estimates of 0.5 grams per joint based on estimates from participants.

To investigate frontolimbic white matter integrity affected by chronic cannabis use and increased depressive symptoms in adolescents and young adults, Shollenbarger and colleagues (2015) set criteria for eligibility slightly lower than previously seen. Criteria for the chronic using group consisted of a minimum of fifty lifetime uses and more than twenty-five joints in the past year (Shollenbarger et al., 2015). Similarly, Medina and others (2007) investigated associations between white matter volume and cannabis use in relation to depressive symptoms using lifetime criteria for the creation of the cannabis-using group. Participants in the user group qualified by reporting at least sixty lifetime uses, and the control group had less than five lifetime uses (Medina et al., 2007). Assessment of such measures and criteria across the literature is imperative to gaining a coherent understanding of the topic as studies use varying definitions, which can only be corrected through effective standardization of the substance. Until such action is taken to understand what a single use is, studies will continue to be incomplete as researchers scramble to create their own definitions. To help further illustrate the variation in how researchers define chronic cannabis use, a table has been included to highlight the differences in methodology (refer to Appendix).

Impact of Cannabis Use on Executive Functioning

Cognition

Past researchers have assessed the impact of adolescent cannabis use on intelligence through a longitudinal twin study with a quasi-experimental approach to account for participants'

family background and genetic properties (Jackson et al., 2016). Users in the same study experienced larger cognitive deficits by late adolescence in measures of verbal ability and general knowledge compared to nonusers (Jackson et al., 2016). Although at baseline assessment, prior to cannabis use, the future users already had significantly lower scores on the subtests than the nonusers in the Minnesota Twin Family Study (Jackson et al., 2016). After adjustment for cohort effects and sociodemographic variables, the cannabis-using group showed an average change in intelligence quotient was 4.0 points lower in the Risk Factors of Antisocial Behavior and 3.4 points lower for users in the Minnesota Twin Family Study. While the users had lower test scores compared to the controls showing a significant decline in crystallized intelligence between follow-ups, there was no evidence of a dose-response relationship between frequency of use and intelligence quotient change. In addition to this finding, the using twins did not show a significantly greater intelligence quotient decline compared to their non-using siblings. Evidence from the samples implies that the declines observed in intelligence quotient may not be a direct result of cannabis use but attributable to familial factors that influence both cannabis initiation and low intellectual fulfillment (Jackson et al., 2016).

Previous researchers also evaluated the neurocognitive functioning of early- and late-onset chronic cannabis users and controls (Fontes et al., 2011). No differences in IQ and vocabulary were found when comparing the early-onset, late-onset, and control groups. However, the investigators found that only the early-onset group performed poorly on selected executive tasks as well as on the frontal assessment battery (Fontes et al., 2011). Results yielded from this study continue to emphasize the significance of age in the onset of cannabis use, and the role it plays in development. Similarly, when Hanson and others (2010) examined the neuropsychological function of cannabis-using adolescents compared to non-using adolescents at

three points over three weeks of abstinence, they found that users performed worse than controls on verbal learning and verbal working memory. In addition, these effects were significant even after controlling for age and socioeconomic status. Findings also indicated that after three days of abstinence, adolescent users learned fewer words than nonusers. However, after two and three weeks of abstinence, the user group performed at similar levels as the controls. While both groups had similar attention processing speeds, users consistently produced lower accuracy than controls on attention/vigilance tasks during the three-week abstinence period (Hanson et al., 2010). A key finding from this study is that deficits in verbal memory and verbal learning may be resolved with abstinence, although attention accuracy seems to persist (Hanson et al., 2010).

The impact of cannabis on cognitive performance has also been associated with related neurodevelopment. Churchwell and colleagues (2010) investigated altered cortical volume and decision-making in adolescent cannabis users, specifically the medial orbital prefrontal cortex, and evaluated impulsivity with the Barratt Impulsiveness Scale. Results from this study indicate that cannabis-using adolescents have decreased right medial orbital prefrontal cortex volumes and increased impulsivity related to decreased future orientation (Churchwell et al., 2010). No significant correlations between volume and measures of cannabis use were detected. However, the volume of the medial orbital prefrontal cortex was positively correlated with the age of first use (Churchwell et al., 2010).

Attention

During adolescence, the brain's systems are not working in uniform, making this period particularly vulnerable to developmental abnormalities as a result of exposure to exogenous cannabinoids (Lubman et al., 2014; Jacobus & Tapert, 2014). The endocannabinoid system has been found to be heavily implicated in synaptic pruning as well as key in white matter

development that occurs during puberty (Lubman et al., 2014). In a review of neuroimaging findings, Wrege and others (2014) found that duration of use, age of onset, and total lifetime use led to negative impacts on executive functioning. Earlier and heavy use resulted in altered structural frontal integrity as well as decreased activations within the superior and middle frontal gyrus. This finding is a possible reason why increased brain effort was needed for users to compete evenly with nonusers on attention tasks. Also, parietal cortices were found to be engaged to maintain attention competence to perform equally. Reduced activity in the anterior cingulate cortex was also found during task performance in chronic users. Tetrahydrocannabinol exposure has been implicated in the acute attenuation of brain regions that typically mediate response inhibition (Wrege et al., 2014).

Chronic cannabis use during early adolescence has also been linked with a reduction in white matter integrity reduction, associated with higher levels of impulsivity. In one neurocognitive study, early and late-onset users were compared with healthy controls (Gruber et al., 2014). The results of this study revealed a significant relationship between the age of onset and severity of microstructural alterations of white matter integrity. Specifically, users in the early onset group have the highest levels of impulsivity. These elevated impulsivity scores may be related to the crossing of fibers throughout the Genu, a bend of the anterior corpus callosum responsible for connecting the medial and lateral surfaces of the frontal lobe, which is interconnected with the anterior cingulate cortex where empathy, impulse control, emotion, and decision making is localized (Gruber et al., 2014). The anterior cingulate cortex and the dorsolateral prefrontal cortex make up the cingulo-fronto-parietal cognitive/attention network which is responsible for executive control, inhibition, attention, and feedback-based decision-making (Gruber et al., 2014). It was concluded that chronic and long-term exposure might cause

significant alterations to this network due to decreased fractional anisotropy within the Genu, particularly because fibers in this region are thinner in comparison to other regions suggesting possible deficits to functions regulated by the cingulo-fronto-parietal cognitive/attention network (Gruber et al., 2014).

Chronic cannabis use has also been linked with decreased fractional anisotropy in temporal areas, impacting attention, working memory, and speed processing (Bava et al., 2010). This reduction in function suggests substance use-related alterations to white matter. During this study, it was also noted that possible compensatory processes take place within the occipital region of users, displaying higher fractional anisotropy associated with improved working memory and complex sequencing performance increased fractional anisotropy was also found in the internal capsule of users, associated with poor verbal memory performance, indicating that neuroadaptive processes may be complicated by competing maturational processes. It also should be noted that the participants in this study had a history of cannabis *and* alcohol use (Bava et al., 2010).

While the previously mentioned studies have found deficits in the speed and quality of attention processes, a study by Nickerson and colleagues (2012) focused on attentional bias. P300 responses were used to measure attentional bias to drug cues as well as self-reported craving and heart rate in cannabis-dependent adolescents. Findings also revealed that P300 responses to cannabis-related visual stimuli were larger than responses to control stimuli suggesting a greater attentional bias to cannabis-related cues. Nickerson and others (2012) found that the handling of cannabis paraphernalia also increased P300 responses as well as self-reported cravings. However, no significant change in heart rate was detected, suggesting heart rates are less sensitive to drug cues (Nickerson et al., 2012).

Memory

The hippocampus is of particular interest because it displays the highest density of CB1 receptors in the allocortex, including very high concentrations within the molecular layer of the dentate gyrus. The dentate gyrus is responsible for the merging of mental representations and memories, making it a critical component in learning (Glass et al., 1997). While other regions of the brain have shown the ability to increase binding capacity after stopping the chronic use of cannabis, the hippocampus is a unique area of concern. This area of the brain does not return to baseline binding capabilities (Hirvonen et al., 2012), resulting in possible deficits in long-term memory storage, as well as cognitive functions associated with this region. After chronic exposure to these exogenous cannabinoids, users displayed possible long-term structural and functional damage in an investigation that found smaller volumes of the right and left hippocampus (Ashtari et al., 2012). Ashtari and colleagues (2012) study showed that these alterations are found to coincide with impaired encoding, storage, manipulation, and retrieval mechanisms. The results also showed that earlier users displayed greater verbal and memory impairments in comparison to the later-onset users. Additionally, chronic users also displayed altered memory related to brain activation in the form of dysfunctional subsequent memory effect production, indicating poor neural efficiency in the area (Ashtari et al., 2012).

A more in-depth investigation in adolescent animals exposed to tetrahydrocannabinol found spatial memory deficits into adulthood, possibly explained by the establishment of less synaptic contacts and/or less efficient synaptic connections in the hippocampus (Rubino et al., 2009). In a study of acutely intoxicated participants, a drop in the performance of free-recall paradigms was recorded, which suggests disruptions to prefrontal circuits as opposed to damage to the hippocampus (Gonzalez, 2007). However, longitudinal studies are required to further

investigate this claim. In a study examining regular cannabis use and memory function by Jager et al. (2011), investigators found no effects of regular cannabis use on adolescent working memory. Investigators did, however, find the working memory system was overactive in users during a novel task, whereas automatization reduced overall activity to the same levels in users and controls (Jager et al., 2011). In abstinent cannabis-using teens, increased levels of activity were detected in the hippocampal and parietal regions during verbal working memory tasks. However, performance levels were normal, implying increased effort was required to maintain a typical score (Jager et al., 2011). Similar conclusions were drawn from a review focused on the effects of cannabis use on memory, noting that increased brain activation is found across the literature in users performing hippocampus-dependent memory tasks (Schoeler & Bhattacarrya, 2013) This increased activation may reflect compensatory mechanisms that could be activated to achieve similar levels of performance as the nonusers (Schoeler & Bhattacarrya, 2013)

Impact of Cannabis Use on Emotional Dysregulation

Another area of vulnerability to exogenous cannabinoid exposure is the amygdala, containing some of the higher levels of CB1 receptors within the brain (McQueeny et al., 2011). While chronic users experience adverse effects, females are found to be particularly vulnerable. Female users had displayed larger right amygdala volumes compared to males, this finding being associated with depression and anxiety linked to greater internalizing symptoms (McQueeny et al., 2011). The prevalence of depression and anxiety was found to increase alongside higher extents of cannabis use, with this pattern being most apparent in female participants (Hall, 2005). Young women who are daily users showed over a fivefold increase in odds of currently developing depression and anxiety compared to nonusers (Hall, 2005). In female teenagers, daily use predicted fourfold higher odds of later depression and anxiety, with weekly use showing a

twofold elevation. However, it is key to note that adolescent depression and anxiety did not predict weekly or daily use (Hall, 2005).

Cannabis use and white matter volume were found to be additive as well as interactive in the prediction of depressive symptoms among adolescents, evident by users having significantly higher scores on the Hamilton Depression Rating Scale. (Medina et al., 2007). This relationship may be in part driven by disruptions to the frontal-limbic basal ganglia circuitry, another area of high CB1 receptor density that is also associated with mood regulation (Medina et al., 2007). Individuals who had met lifetime criteria for cannabis dependence saw an increase in odds of major depressive disorder, suicidal ideation, and attempted suicide by 1.3-3.4 versus their non-cannabis dependent twin, specifically before the age of 17 (Lynsky et al., 2004). However, in a longitudinal study of college students, researchers found chronic users experienced fewer days of impairment in relation to illness and emotional problems as well as fewer visits for mental health compared to late-increasing users during college (Calderia et al., 2012). This finding did not coincide with the rest of the results, as the chronic group fared significantly worse on nine out of the ten outcomes tested (Calderia et al., 2012).

White matter integrity within frontolimbic pathways has also been thought to mediate apathy symptoms among regular cannabis users (Shollenbarger et al., 2015). Poor white matter integrity was found to be significantly associated with an increase in self-reported symptoms of depression and apathy in regular users (Shollenbarger et al., 2015). In a study of the Northern Finland birth cohort of 1986, Mustonen and others (2021) reported modest associations between adolescent cannabis use and an increased risk of future depression and anxiety disorder. Statistically significant associations were reported between adolescent cannabis use and depression and anxiety disorders after adjustment for baseline externalizing and internalizing

symptoms. These results suggest that the use of cannabis may increase the risk of depression and anxiety disorders independently of adolescent psychopathology (Mustonen et al., 2021).

Further, Lynskey and colleagues (2004) conducted a cross-sectional survey of twin pairs discordant for lifetime cannabis dependence and those discordant for early cannabis use. Results indicated a moderate degree of comorbidity between cannabis dependence and measures of mental health (Lynskey et al., 2004). Individuals who met lifetime criteria for cannabis dependence had 1.3 to 3.4 times higher odds of major depressive disorder, suicidal ideation, and attempted suicide compared to their non-cannabis dependent co-twin (Lynskey et al., 2004). In a study conducted by Degenhardt et al. (2012) describing patterns of cannabis use and their changing associations with mental health issues during fifteen years of follow-up, investigators found no strong evidence of an association between adolescent cannabis use and major depressive episodes at age 29. Heavier adolescent cannabis use was more consistently associated with a twofold higher risk of an anxiety disorder at 29, specifically if cannabis use continued at this age. Results most clearly depicted that early regular use in adolescence increased risk of anxiety disorder at age 29, with a higher risk if regular use persists. Another key finding from this study is that there was an increased risk of anxiety disorders at age 29 in adolescent cannabis uses even if they stopped using cannabis in adulthood (Degenhardt et al., 2012).

Future Directions

The field of cannabis study, particularly that of cannabis use in adolescents, is still new, with much to learn about the topic yet. Current research has provided a foundation for areas of focus within adolescent cannabis use, such as investigating cognitive deficits conducted by Jackson and colleagues (2016), finding impairment in verbal ability and general knowledge. Abnormalities documented in adolescent development across the literature raise alarms for the

next generations with consistent findings of greater internalizing symptoms, attentional issues, and general memory impairments (Mustonen et al., 2021; Wrege et al., 2014; Ashtari et al., 2012). It is hypothesized that these impairments are due to disruptions in neural circuitry throughout the brain, specifically portions with higher levels of CB1 receptors (Glass et al., 1997; Hirvonen et al., 2012). As steps are taken to federally decriminalize cannabis, the importance of this research continues to rise in demand as the numbers of reported users fluctuate, such as the 15.9% increase from 2018-2019 (McCance-Katz, 2020) as well as annual use in college students reaching the highest levels seen in over thirty-five years (NIDA, 2021).

Researchers should continue to investigate several aspects of adolescent cannabis use with an emphasis on the age of onset but also the quantity consumed per session as disparities between parameters of use persist, with investigators using seemingly arbitrary numbers in defining what qualifies as chronic use. To pursue this consistency requires regulation of cannabis like that of alcohol, which has clear measures of what defines one drink. This regulation will be key in future research, helping to narrow the wide-ranging measures used across studies to produce more reliable results in understanding the impacts of chronic use. Further investigation should also be conducted on the understanding of the endocannabinoid system and the roles it plays in neural development. By understanding how this system regulates brain development, researchers can place a heavier focus on adolescents in the most vulnerable phase and continue to educate and warn the youth of the dangers present in early and chronic use.

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Appendix

Table 1

Description of Human Neurological and Genetic Studies Reviewed

Study	Brain Imaging & Data Collection	Parameters for Cannabis Use	Study Type
Ashtari et al., 2012	MRI	Average 5.8 joints daily	Cross-Sectional
Bava et al., 2010	DTI	180 and 1,800 instances of marijuana use and 50 and 700 instances of drinking	Cross-Sectional
Becker et al., 2010	fMRI	10 grams lifetime use	Cross-Sectional
Caspi et al.,	Genetic testing	Cannabis use < age 15 or monthly cannabis use by age 18	Longitudinal
Churchwell et al., 2010	MRI	DSM-IV cannabis dependence	Cross-Sectional
Gilman et al., 2014	MRI	1 use per week	Cross-Sectional
Gruber et al., 2014	DTI	2,500+ lifetime use, use 5 out of last 7 days	Cross-Sectional
Hirvonen et al., 2012	PET	Daily for at least 5 years	Cross-Sectional
Jackson et al., 2016	Intelligence	30+ uses	Longitudinal twin study
Jacobus & Tapert, 2014	ASL	>200 lifetime uses	Cross-Sectional
Jacobus et al., 2015	MRI	>100 lifetime uses	Longitudinal
Jager et al., 2010	fMRI	200+ lifetime uses	Cross-sectional
Jager et al., 2013	fMRI	2-10 joints per day	Cross-Sectional
McQueeny et al., 2011	MRI	Determined through interview	Cross-Sectional
Medina et al., 2007	MRI	60+ lifetime uses	Cross-Sectional
Meier et al., 2019	MRI	Multi-informant screening to assess conduct problems	Longitudinal
Shollenbarger et al., 2015	MRI	50+ lifetime joints, 25+ past year joints	Cross-Sectional

Note: MRI - Magnetic Resonance Imaging; DTI - Diffusion Tensor Imaging; fMRI - Functional Magnetic Resonance Imaging; PET - Positron Emission Tomography; ASL - Arterial Spin Labeling.