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The Chronic Effects of Cannabinoid Use on the Prefrontal Cortex in Adolescence Compared to Adulthood: A Literature Review

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Abstract
Adolescent cannabis use has become a significant public health concern due to increasing legalization and usage rates. This review examines recent clinical and preclinical research on the effects of chronic cannabis use during adolescence compared to adulthood, with a focus on prefrontal cortex development. Adolescence is a period of development that includes not just sexual development and puberty but also essential brain maturation. This brain development is characterized by gray matter pruning, increases in white matter, and altered development within the endocannabinoid system. Evidence suggests exogenous cannabinoids, such as Delta 9-Tetrahydrocannabinol (Δ^9THC) and cannabidiol (CBD), can disrupt the normal neurodevelopmental processes in adolescents, particularly in the prefrontal cortex. Previous research, including neuroimaging studies, has found that cannabis use during adolescence is associated with altered cortical thinning patterns, especially accelerated thinning in prefrontal regions involved in executive functions. Earlier onset of use also correlated with pronounced structural alterations. Behaviourally, early use of cannabis is linked to deficits in attention, memory, and executive functions, with conflicting results on whether these factors are reversible after cessation of cannabis use. Rodent models assessed also corroborated the results found in clinical studies, demonstrating THC exposure can induce long-lasting impacts in prefrontal-mediated behaviours and neuroplasticity, which is not seen in adult cannabis users. The endocannabinoid system plays a key role in this neurodevelopment, and the disruption caused by exogenous cannabinoids during adolescence may alter typical development. Proposed mechanisms include possible premature synaptic pruning, disrupted white matter development, and lasting neurochemical imbalances. A previous meta-analysis demonstrated that some structural and functional changes may recover with abstinence; however, early, heavy use appears to risk persistent neurocognitive deficits. Further research is needed to clarify dose-dependent effects and interactions with other substances. Overall, accumulating evidence suggests adolescent cannabis exposure may induce lasting changes in brain structure, function, and behaviour not observed with adult use.

Keywords: recreational cannabis use; adolescence; brain development; endocannabinoid system; THC; CBD; prefrontal cortex; chronic use; behavioural changes; substance abuse

Introduction

Cannabis has historically been used for medicine and religious practices, with the understanding that active chemicals, such as Delta 9-Tetrahydrocannabinol (Δ^9THC) and Cannabidiol (CBD), can lead to benefits and the development of therapeutics [1, 2]. Benefits from use include its use as an anti-inflammatory, antibiotic, and anaesthetic agent [1, 2]. Recent studies have supported that cannabinoid use may result in long-term cognitive and structural impairments of the prefrontal cortex [1, 3–5]. The effects of cannabinoids on the body have become an expanding and thriving topic of interest in biomedical sciences. There have been discussions on the possible negative impacts on adolescent psychosocial development and lingering cognitive impairment after prolonged cannabinoid use [2].

The impact of cannabinoids on neuronal networks has become increasingly important due to the increased use of cannabinoids in adolescents, with many reporting their first-time use being within the 12-20-year age range [3]. A large concern for the neurological development of the prefrontal cortex (PFC) exists in this population, especially for chronic users [4]. The possible effects of early cannabinoid use were found to differ from cannabinoid initiation later in life. Additionally, evidence from animal and human studies indicated the sensitivity of the adolescent period for brain development, increasing its susceptibility to the neurocognitive effects of cannabis [5]. A deeper understanding of the impact of age of onset during adolescence compared to adulthood would help further the knowledge of how age relates to cannabinoid use.

With this knowledge, a review of the current longitudinal research will help distinguish the effects of early cannabinoid use from those of adulthood. Based on a variety of articles that range from research articles to literature

reviews, many have come to the premise that chronic cannabinoids can affect the developing PFC long-term [6–8]. This review aims to explore the chronic effects on the PFC from cannabinoid use during adolescence and adulthood, to identify common and contradicting themes, as well as identify the gaps in the current research and provide an overview of the current body of knowledge while inspiring ideas for future studies.

Adolescence, A Critical Period for Prefrontal Cortex Development

Adolescence is the transitional period between childhood and adulthood, typically defined by the World Health Organization as ranging from 10 to 19 years of age, characterised by changes to social and cognitive abilities before gaining the independence and skills of an adult [9, 10]. Among these changes, the prefrontal cortex, proposed to underlie the maturation of executive functioning, is one of the latest brain regions to mature in humans. This ongoing development is subject to constant neurophysiological changes, such as synaptogenesis and pruning, and can be a sensitive period for external insults before reaching maturity in the mid-20s [10–12].

The endocannabinoid system is highly active during adolescence, where cannabinoid receptors 1 (CB1Rs) undergo constant reorganisation. Due to CB1Rs being densely localised throughout the brain, and cannabinoids being prime agonists of CB1Rs, cannabinoids are believed to impact brain regions involved in learning, memory, and the PFC [6, 13]. CB1Rs play a role in brain maturation and in maintaining homeostasis through GABAergic activations and other means. Impairments to the CB1Rs' signalling may cause long-term prefrontal disinhibition [14]. Within subdomains of the PFC, the development of dendritic trees and the density of spines take time to mature because of their complexity, which involves pruning. Proper maturation is important for proper signalling in the PFC pyramidal neurons [7, 8, 15].

Cannabinoids

Most cannabinoids used in the relevant studies are those associated with addictive properties and long-term side effects. Chronic cannabinoid exposure has been shown to induce region-specific desensitisation & downregulation of CB1Rs, which contributes to the development of tolerance and withdrawal symptoms during cannabis use [16, 17]. Δ^9-THC is a phytocannabinoid that is related to altered mood, psychotic behaviour, and continued substance use, and has been the typical active substance used by adolescents [18]. There are synthetic cannabinoids that mimic the effects of Δ^9-THC and can have serious side effects; however, they are not widely studied [19, 20, 21]. Given the many options for the types of cannabinoids, this review will focus mainly on those that adolescents have the most access to, Δ^9-THC vs synthetic cannabinoids [19–21].

Methods

A comprehensive literature search was conducted using the following databases: PubMed, PsycINFO, Google Scholar, and Scopus. The search terms included "recreational cannabis use," "adolescents," "brain development," "endocannabinoid system," "prefrontal cortex," "chronic use," and "behavioural changes." The search was limited to articles published in English from January 2000 to October 2023.

Studies were included if they examined the effects of cannabis use on brain development in adolescents, including both clinical and preclinical (animal model) studies, focused on changes in the prefrontal cortex related to cannabis use, and were peer-reviewed and published in reputable journals. Studies were excluded if they did not specifically address the age of onset of cannabis use, were case reports, opinion pieces, or were not available in full text.

Data were independently extracted and verified for accuracy by the authors. The extracted information included study design, sample size, age of participants, duration and frequency of cannabis use (when reported), and key findings related to brain structure and function.

The findings from the included studies were synthesized narratively, with a focus on identifying common patterns and discrepancies. The review also highlighted gaps in the current literature and suggested directions for future research.

Results

Human Studies on Chronic Effects of Adolescent Cannabinoid Use

Previous animal studies have indicated the effects of early cannabinoid use on the neurodevelopment of the adolescent brain. The effects include structural, neurodevelopmental, and behavioural changes [6]. The applicability of these findings to humans on a large scale can be observed through longitudinal studies.

Structural and Functional Changes

Albaugh et al. [3] investigated the relationship between cerebral cortical thickness development, measured using magnetic resonance imaging (MRI), and cannabis use in adolescents. They found that cannabis use in adolescents [1–19] was correlated with sped-up cortical thinning primarily in the prefrontal cortex; specifically in regions that typically would undergo structural development during this time and had high CB1R availability. Larger doses (0->40 lifetime uses) were found to be associated with increased thinning of the PFC than in individuals who used lower doses (1-9 lifetime uses). PFC thinning also had an association with the participants' impulsiveness. Limitations included measuring typical CB1R availability in a different sample from the study's participants, making it difficult to definitively support that the thinning was in areas with high CB1R availability. The study also used self-reported data on cannabis use, which limited accuracy. The types of cannabis

products used were also not accounted for. With these findings on the effect of early cannabis use onset on neurodevelopment, the persistence of these effects into adulthood and the question of whether later onset leads to different consequences are brought up.

These findings were further addressed by the Albaugh et al. [22] longitudinal study, where they investigated the differences in cannabis initiation during adolescence (14-19 years) compared to young adulthood (19-22 years) on cortical thickness and behaviour. They affirmed the negative association between adolescent cannabis use and cortical thickness in the PFC. The negative effects persisted into young adulthood (22 years old).

Initiation during adolescence was associated with cortical changes in the dorsolateral and ventrolateral areas of the PFC and was also correlated to have continued effects into adulthood and had partial mediation of the association between cannabis use during adolescence, and cannabis, cocaine, and ecstasy use in the past month at 22 years of age. However, it can not be said with complete certainty that the cortical changes are related to cannabis use instead of the possible existence of another neurodevelopmental path.

Multiple other studies have used MRI scans and shown similar results with the use of cannabis and the progressive loss of PFC thickness [23, 24]. These multiple associations across studies between cannabis use and the loss of areas rich in CB1Rs, including thinning PFC, may suggest that cannabis use plays a strong role in PFC thinning, one of the many consequences of chronic cannabis use in adolescence.

Neuropsychological Assessments on Early Onset Cannabinoid Use

Schuster et al. [13] concluded that the early onset of marijuana use was associated with learning weaknesses through the use of neuropsychological assessments. Results showed that those with earlier cannabis initiation before the age of 16 years recalled fewer words compared to groups who initiated cannabis use after the age of 16 years, and the control group. Schuster et al. [13] suggest that these results observed in adolescent marijuana users may result from memory network impairments caused by disruptions in the areas where CB1Rs and anandamide (endogenous cannabinoid) are localized in the PFC. This may be a result of weakened executive function, which is largely contributed to by the PFC. The limitations of this study may involve the difference in learning average between groups. Overall, this study may contribute to a common underlying mechanism against the developing PFC from cannabinoid use by disruptions of CB1Rs and the associated development of the endocannabinoid system in adolescence. Agreeing with previous studies on the association between PFC thinning and cannabis use, this suggested that PFC thinning may lead to memory network impairment due to alterations of the CB1R population.

Meta-Analysis of Lasting Cognitive Effects

Conversely, a comprehensive meta-analysis by Scott et al. (2018) examined 69 studies involving 2,152 cannabis users and 6,575 comparison participants to investigate the relationship between cognitive function and regular cannabis use in adolescents and young adults. The analysis revealed a small but significant overall effect size (d = -0.25; 95% CI, -0.32 to 0.07) for reduced cognitive functioning associated with frequent or heavy cannabis use. Interestingly, studies requiring an abstinence period longer than 72 hours showed a very small, non-significant effect size (d = -0.08, 95% CI, -0.22 to 0.07), which suggested potential reversibility of cognitive deficits with prolonged abstinence [11]. These findings differ from the neuropsychological and structural studies, but they indicate the complexity of the relationship between cannabis use and cognitive outcomes in adolescents. However, it is important to note that while meta-analyses provide valuable insights, large longitudinal studies would be more indicative of possible changes over time. The authors also emphasized that for most individuals, the observed cognitive deficits may be of questionable clinical significance, especially after sustained abstinence [11].

Comparisons to Adult Cannabinoid Use

Studies that involve the inclusion of adult-treated groups can be used to control for specific effects only found because of cannabinoid use during adolescence, which provides emphasis on the vulnerability period of adolescence. In the study done by Albaugh et al. [22], cannabis initiation in adolescence was associated with speeding up the cortical thinning in age-related areas of the dorsolateral and ventrolateral portions of the PFC. These findings contrast with studies on cannabis initiation in young adults, which have shown a reduction in age-related cortical thickness increases in heteromodal association areas, medial paralimbic regions, and the left temporal areas of the prefrontal cortex (PFC). In the Schuster et al. [13] study, late-onset marijuana users showed no significant learning deficit compared to the control group, when there was a stark difference in the learning deficits found in early-onset users. These studies suggested that cannabinoid use during different periods of life could lead to different outcomes, placing importance on understanding the vulnerability period during adolescence and emphasizing the importance of age of onset as a contributing factor.

Rat Studies on Structural Effects of Adolescent Cannabinoid Use

The use of rat studies is helpful due to the added benefit of control compared to human studies. With rats, studies can control drug use, the age of initiation, and the duration of cannabinoid use [25]. This helps provide a clearer view of a possible relationship between the age of onset and cannabinoid-related deficits to cognitive abilities and brain structure.

Δ⁹-THC Exposure to Adolescent Rat Models

The effects of Δ⁹-THC have been studied extensively as the main psychoactive constituent of cannabis. A study reported that Δ⁹-THC exposure in adolescent rats induces long-term loss of GABAergic inhibition function in the PFC [14]. Results showed lower expression levels of GAD67, indicating reduced GABAergic levels in the medial prefrontal cortex (mPFC) in adolescent rats compared to adult rats. This aligned with the results of the increased mPFC pyramidal neuron activity and bursting rates from in vivo electrophysiological recordings, suggesting impairments to the inhibitory feedback within the PFC circuit [14].

Miller et al. [26] investigated how adolescent Δ⁹-THC exposure was associated with PFC maturation in an animal model. They found lasting effects on the dendrites and altered neurodevelopment of the rats. This was concluded due to the early pruning of dendrite spines and the death of dendrite arbours early in adulthood. This could be the underlying mechanism leading to cannabis-associated cortical thinning in individuals with early onset of cannabis use.

Synthetic Cannabinoids and Their Effect on the Developing PFC

Besides the significant interest in studying the effects of Δ⁹-THC, synthetic cannabinoids are studied as well and are similar in the negative aspect of detrimental long-term effects on adolescent PFC. A study has demonstrated lasting impairments to the long-term potentiation (LTP) on the postsynaptic level primarily in the PFC in adolescents with chronic use of CP 55 940, another type of synthetic cannabinoid [6]. Results also showed reduced numbers of dendrites and their total length in layer II/III pyramidal neurons of the PFC in adulthood, demonstrating both negative long-term structural and functional effects from CP-treated adolescent rats [6].

Another synthetic cannabinoid, JWH-018, has been found to have multiple chronic effects on the PFC [27]. Results led to a significant decrease in prepulse inhibition (PPI) of the startle reflex, a significant decrease in parvalbumin-expressing (PV) GABAergic interneurons surrounded by perineural networks, and enhancement of microglia soma, suggesting more reactivity observed in the prefrontal cortex, in male mice. However, adolescent female rats treated with JWH-018 show no significant changes compared to the female control group for all cases [27]. Discrepancies between male and female adolescent rats from cannabinoids may suggest differences in the developmental speed of the PFC and can affect the results of studies if not accounted for.

Contrasting results have been found in a study using HU-210, another synthetic cannabinoid, on adolescent rats. Altered anxiety-like behaviour was not found using elevated plus maze (EPM), open field, social interaction, modified forced swim, and sucrose preference tests as opposed to Δ⁹-THC studies known to be widely used for long-term consequences of adolescent cannabis exposure [19]. Though not readily accessible for human adolescents to use, the gap in knowledge of synthetic cannabinoids is evident, and needs to be studied further for their effects on the PFC.

Adult Rat Studies

Cannabinoids used for adolescent rat studies have shown similar negative impacts on the function and neurological makeup of the PFC as they progress to adulthood, with certain studies straying from the rest. Though it is becoming known that cannabinoids taken chronically during adolescence can lead to lasting effects on the developing PFC; it is better to have a baseline of how the cannabinoids affect the PFC in adult rats to emphasise the impact cannabinoids have during the vulnerability period in adolescents.

The study found a long-term decrease in the PPI of the startle reflex during adulthood in adolescent-treated rats. A parallel experiment was also done in that study on adult-treated rats and found no changes to the PPI compared to the control group [21]. This provides an assessment of the increased accuracy of the adolescent PFC vulnerability period and the extent of cannabinoid effects on the PFC.

Discussion

During the highly developing period of adolescence, numerous clinical and pre-clinical studies indicated an association between the early onset of cannabinoid use and negative effects on the structure and neuronal networks of the PFC, affecting behaviour and cognitive abilities. Cortical areas with many CB1Rs and cortex thickness changes due to age show indications that cannabis use during adolescence may cause serious neurodevelopmental changes well into adulthood [3, 22–24]. This could be caused by the early pruning and premature death of dendritic spines from chronic cannabis use [6, 26]. Chronic cannabis use has shown disruptions of rich CB1Rs, impairing inhibitory feedback of the PFC, which leads to impairment of the memory network [13, 14, 27]. This can be explained by the importance of proper development of the endocannabinoid system, which is highly active during adolescence to regulate excitatory/inhibitory inputs in the PFC through CB1Rs [6, 13].

Based on these longitudinal studies, there is evidence that early cannabis initiation is linked to decreased cortical functioning and structural changes. There is also a possible association between the cortex's structural development and the behavioural changes found in cannabis users. However, multiple factors, aside from the age of onset, also affect the consequences of ongoing cannabis use, including frequency and intensity of use, Δ⁹-THC concentration of the product, sex differences, and duration of abstinence [2, 11, 28]. With these results in mind, cannabis use during adolescence should not be seen as reasonable and should be prevented. The impacts seen on cognition and the increased likelihood

of cannabis being a 'gateway drug' for early users also indicate the importance of communicating the possible harms that come with cannabinoid use to this population [2].

The analysis of the review is limited due to the differing definitions of heavy cannabinoid use and the differing definitions of what age range constitutes adolescence across articles. To reach better conclusions that can be communicated to the appropriate community, these factors should be standardised within the field. Additionally, a previous review [18] noted that many articles did not have a proportionate number of men and women in the groups reviewed. This is an issue due to the indication of sex differences in cannabis use effects [28].

Despite this limitation not being a concern in most of the reviewed articles, continuing to address these limitations in future research will enhance the reliability and applicability of findings, ultimately contributing to a more comprehensive understanding of the impact of adolescent cannabis use.

Conclusion

Although cannabinoids are not perceived to be as dangerous as other substances, recent research has identified cannabis use during adolescence as being linked to long-term changes and deficits. This study is crucial to the field as it highlights the multifaceted impact of early cannabinoid use on the PFC, including structural changes and the resulting cognitive and neuropsychological deficits. The timing of initiation plays a significant role in determining these outcomes, emphasizing the need for targeted education and intervention strategies for adolescents. The findings underscore the importance of discussing the differential effects of cannabis use between adolescents and adults, which many young users may not be aware of.

These studies raise new research questions, such as the specific mechanisms through which cannabinoids affect brain development at different stages and the potential for reversibility of these changes with cessation of use. Future research should focus on investigating the established changes made to neuronal networks in the PFC and their relationship to the exhibited behavioural changes in those who initiated cannabinoid use during adolescence. Whether the PFC neuronal network changes explain the behavioural changes is yet to be determined.

However, future studies should account for confounding factors such as, but not limited to, sex, age of onset, and use duration, with a good metric for the age of onset that is indicative of the age of adolescence. Additionally, longitudinal studies will allow the tracking of the long-term effects of adolescent cannabis use into adulthood and assist in the development of effective targeted prevention and intervention programs. With an increase in studies done to increase understanding of typical brain development in adolescence and young adulthood, the effects of substances such as cannabis can be assessed with a better understanding and accuracy.

List of Abbreviations

CB1Rs: cannabinoid 1 receptors
CB2: cannabinoid 2
EPM: elevated plus maze
LTP: long-term potentiation
mPFC: medial prefrontal cortex
MRI: magnetic resonance imaging
PFC: prefrontal cortex
PPI: prepulse inhibition
PV: parvalbumin-expressing
Δ⁹-THC: Delta-9-Tetrahydrocannabinol

Conflicts of Interest

The authors declare that they have no conflict of interest.

Ethics Approval and/or Participant Consent

This study did not require ethics approval or participant consent as it is a literature review examining previously conducted studies.

Authors' Contributions

NM: contributed to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.
JN: contributed to study design and planning, assisted with the collection and analysis of data, and gave final approval of the version to be published.

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