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MINI-REVIEWS

Cannabis in Adolescence: Lasting Cognitive Alterations and Underlying Mechanisms

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Abstract

Cannabis consumption during adolescence is an area of particular concern, owing to changes in the social and political perception of the drug, and presents a scientific, medical, and economic challenge. Major social and economic interests continue to push toward cannabis legalization as well as pharmaceutical development. As a result, shifting perceptions of both legal and illicit cannabis use across the population have changed the collective evaluation of the potential dangers of the product. The wave of cannabis legalization therefore comes with new responsibility to educate the public on potential risks and known dangers associated with both recreational and medical cannabis. Among these is the risk of long-term cognitive and psychological consequences, particularly following early-life initiation of use, compounded by high-potency and/or synthetic cannabis, and heavy/frequent use of the drug. Underlying these cognitive and psychiatric consequences are lasting aberrations in the development of synaptic function, often secondary to epigenetic changes. Additional factors such as genetic risk and environmental influences or nondrug toxic insults during development are also profound contributors to these long-term functional alterations following adolescent cannabis use. Preclinical studies indicate that exposure to cannabinoids during specific windows of vulnerability (e.g., adolescence) impacts neurodevelopmental processes and behavior by durably changing dendritic structure and synaptic functions, including those normally mediated by endogenous cannabinoids and neuronal circuits.

Keywords: cannabis; adolescence; cognition

Introduction

Cannabis consumption during adolescence is an area of particular concern, owing to changes in the social and political perception of the drug, presenting a scientific, medical, and economic challenge. Major social and economic interests continue to push toward cannabis legalization as well as pharmaceutical development. As a result, shifting perceptions of both legal and illicit cannabis use across the population have changed the collective evaluation of the potential dangers of the product. The wave of cannabis legalization, therefore, comes with new responsibility to educate the public on potential risks and known dangers associated with both recreational and medical cannabis.

The Determinant Role of the Adolescent Developmental Period in Neurodevelopmental Diseases

In humans, adolescence is a period of life characterized by a number of developmental changes, which occur

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between childhood and adulthood.[1] Although age is not a strict marker of the adolescent timeframe, the age-range for this period is roughly defined as 10–19 years in humans.[2] In comparison, puberty is a relatively short period of which the main clinical developments include sexual maturation and growth acceleration. Cognitively and behaviorally, adolescence is characterized by improvements in intelligence quotients, working memory, and problem solving to prepare adolescents for adulthood, and by the appearance of specific behavioral phenotypes such as risk taking, sensation seeking, and intense peer socializing.[3,4]

Brain maturation is a process that begins following conception and continues throughout adolescence and into adulthood. Neuronal plasticity, which allows alteration of connections between neurons through synaptic long-term potentiation (LTP) or depression (LTD), plays a major role in integrating environmental information and physiological changes. During adolescence, the brain matures through sensitive periods, which occur at different times varying by brain region. The term "critical period" refers to a restricted sensitive time period wherein maturational changes are particularly sensitive and rapid.[5] Beyond these periods, neurocognitive development is characterized by synaptic pruning and increased myelination, particularly in the frontal, parietal, and temporal regions.[6] The prefrontal cortex (PFC), which regulates the highest executive functions in humans, exhibits the largest overproduction of synapses and the slowest rate elimination of all examined regions.[5]

This period of profound neurodevelopmental change is accompanied by increased vulnerability to substance use. However, most adolescents do not use drugs, and those who do are often exposed to different factors than those who remain abstinent. Additionally, some users maintain moderate use for decades, while others have intermittent periods of cessation, or escalate rapidly and develop substance use disorders. Thus, no single factor is sufficient to explain the progression to harmful substance use, and only a critical combination of risk factors and/or absent protective factors triggers harmful substance use behavior. The threshold beyond which inappropriate substance use behavior may be triggered is unique to each individual and may be impacted by several potential combinations of external and intrinsic elements. Human behavior is therefore considered the result of the "biological embedding" of social and environmental conditions.[7]

The main individual characteristics that may contribute to inappropriate substance use are genetic susceptibilities, personality traits (sensation seeking, aggression, and impulsivity), mental health problems (post-traumatic stress disorder, attention deficit/hyperactivity disorder, depression, anxiety, antisocial personality, etc.), cognitive impairments, head traumas, language delays, decision-making difficulties, emotional regulatory deficits, and adjustment difficulties.[8–10]

Macrolevel socioenvironmental influences that may interact with these characteristics in adolescence are mainly due to lack of economic and social resources (poverty, homelessness, lack of access to care, child labor) and maladaptive social environment (antisocial norms, social exclusion, conflict/war, etc.).[11,12] Significant influences at the individual level are related to the family (abusive or neglectful parenting, stressful environment, negative role modeling, lack of monitoring, parental substance abuse), school (poor quality early education, negative school climate, lack of prevention programs, etc.), and peer influences (antisocial peers, substance use, social network influence, etc.).[13,14]

Stress is one common denominator among these factors and is now recognized as able to impact both the hormonal and neural systems that regulate learning, memory, decision making, and other functions during adolescence, which normally support adaptive behaviors. The involvement of hormonal factors is differentially impacted in stress behavior of boys and girls; the latter more readily resorting to substance use to limit stress symptoms.[15,16]

Addiction thus presents as a complex phenotype regulated by genetic and socioenvironmental factors. Environmental information, recognized by the brain and peripheral tissues, elicit a response, which often involves changes in gene expression. These interactions are delayed by epigenetic mechanisms, including histone modifications, DNA methylation, and expression of noncoding RNAs and non-long noncoding RNAs. These alterations disrupt certain physiological responses, including synaptic plasticity and stress hormone secretion.[17] Ultimately, early life socioenvironmental experiences may modify gene expression through epigenetic processes, thus explaining individual differences in responses to stress and trauma and in the development of substance use disorders.

Clinical and Epidemiological Data

With the exception of tobacco and alcohol, cannabis is the most widely used drug among young people, defined by the United Nations as those between 15 and 24 years of age.[7,18] The perceived innocuity of cannabis

combined with increasing access to the drug are likely drivers of its prevalent consumption in the youth population. Prevalence of past-year and past-month use are indicators of recent and regular use: in 2018, it is estimated that there were 13 million past-year users of any drug among students 15–16 years of age in the world, with an estimated 11.6 million past-year users of cannabis. This corresponds to an annual prevalence of cannabis use of 4.7% among this age group—a rate that is higher than the rate among the general population 15–64 years of age (3.9%). In 2018, past-year use of cannabis among young people 15–16 years of age was notably elevated in Oceania, the Americas, and Europe (17.8; 12.1%, and 11.7%, respectively). In 2020, 43.7% of high school seniors in the United States reported having used cannabis in their lifetime.

More worryingly, the prevalence of heavy cannabis use in adolescence has tripled over the past 25 years, with 6.9% of US high school seniors reporting daily use.[19] Approximately 9% of all people who experiment with cannabis develop cannabis use disorders, compared with >16% of those who initiate this use during adolescence.[20]

Boys, who exhibit higher rates and frequency of cannabis use compared with girls, also employ a greater variety of routes of administration of cannabis and are more likely to consume high-potency products and/or cannabis concentrates. These patterns of use have been linked to greater risk of developing cannabis-use dependence.[21] Nevertheless, the gap between men and women has narrowed in recent years, especially among teenage users.[22] In addition, women show a "telescoping effect," which results in a more rapid progression of first use to cannabis use disorder.[23]

Widespread decriminalization and legalization of cannabis have contributed to significant changes in the landscape of consumption. In the United States, medical and recreational legalization of cannabis correlates strongly with both rates of cannabis consumption and concomitant psychiatric consequences such as cannabis use disorder.[24] Over the last two decades of regulatory changes, potency of cannabis and cannabis extracts has also increased significantly.[25] These trends are mirrored outside of the United States, as well as in Europe.[26] While no significant trends in age-of-onset for first cannabis consumption have been noted over this period, a small decrease in overall adolescent cannabis consumption was observed.[27] Notably, the route of administration has shifted progressively from smoking to oral (edible) consumption and vaporization. Together with changes in the biodynamic makeup of cannabis (e.g., increased THC content and decreased associated phytocannabinoids), these factors may be important considerations in understanding the consequences of adolescent cannabis use.

While repeated associations between early initiation of cannabis use and later-life drug abuse disorders have been suggested (e.g., "gateway theory"), lifetime trends of drug use following initiation with cannabis as compared with other psychoactive substances has failed to confirm a unique role for cannabis in spurring a progression to further differentiated drug abuse.[28,29]

Cannabis use is typically initiated in late adolescence and peaks in young adulthood. Before the age of 16, cannabis use has been linked to increased risks of acute harm and susceptibility to drug use disorders and mental health disorders, including personality disorders, anxiety, depression, and suicidality.[30,31] Acute cannabis consumption, even in infrequent users, can generate a range of negative mood states, including feelings of anxiety, tension, agitation, mental confusion, memory impairment, unsteadiness, suspiciousness, and paranoia.[20]

Both observational and experimental studies have confirmed the influence of cannabis use on the initiation and persistence of psychotic disorders, such as schizophrenia and bipolar disorder. These adverse effects observed after acute or regular use of cannabis have been strongly correlated with the concentrations of THC in the consumed product, which have been rising dramatically for several decades. Moreover, concentrations of cannabidiol (CBD), whose protective effects against some negative psychological THC effects are now well described, are decreasing.

According to some authors, the increase in the ratio THC:CBD may be the reason for the increase in harmful effects associated with cannabis use.[32] Similarly, the use of potent synthetic cannabinoids, often supplanting THC, enhances the risk of neuropsychological side effects.[33,34] Early initiation of cannabis use among adolescents is dose dependently associated with the emergence and severity of psychotic symptoms and functional impairment, such that adolescents who initiate use earlier and use more frequently have poorer disease and treatment outcomes.[35] The relationship between developmental cannabis exposure and later-life emergence of mental health disorder symptoms is especially strong in people with particular genetic polymorphisms, suggesting that cannabis use interacts with genotype to increase mental health risk.[36]

Pre-clinical Approaches: Rodents and Primates

Pre-clinical approaches using rodent or nonhuman primate models to examine the neuropsychiatric effects of neurodevelopmental cannabinoid exposure offer many advantages over long-term clinical studies.

First, it is possible to exert precise experimental control, both temporally and in dosing consistency, of the cannabinoid in question throughout the entire course of exposure. This level of precision is impossible in human clinical investigations relying on subject self-reporting of historical cannabis use patterns. Indeed, self-reported rates of cannabis consumption are particularly inaccurate in adolescents, as consumption of cannabis has been legalized only for adults and therefore adolescents or juveniles are likely to underreport cannabis use.[37] Second, pre-clinical models allow for the precise interrogation of specific neural circuits, neuronal populations, and molecular biomarkers that would be difficult to obtain from human subjects. Finally, pre-clinical cannabinoid exposure models can assess multiple routes of cannabis exposure, ranging from systemic injection procedures to regionally specific direct infusions, and inhalation and/or edible consumption methods.

Although generally overlooked, it should be kept in mind that comparison of the pharmacokinetic properties of Δ9-THC have revealed many differences in THC distribution and metabolism between adolescent and adult (male) mice.[38] Numerous pre-clinical studies have demonstrated that nonhuman primates, when exposed to stringent protocols involving prior substance addiction (i.e., self-administration preconditioning with noncannabinoid substances) or some degree of reward/coercion (i.e., pairing cannabinoid self-administration with additional rewarding parameters), self-administer THC through intravenous administration.[39] Activation of CB1Rs produces strong rewarding effects and regulates conditioned aversion learning and memory formation in brain circuits such as the mesolimbic pathway in various rodent behavioral models.[40,41]

Importantly, CB1R transmission has been shown to directly regulate emotional salience processing through functional modulation of dopaminergic neuronal activation states. For example, CB1R transmission in the rodent PFC was shown to biphasically modulate subcortical DA neuron activation states in the ventral tegmental area (VTA); low acute doses of CB1R agonists caused hyperactivation of DA firing and bursting frequency and a corresponding amplification of normally nonsalient fear-conditioned associative memories. Higher doses of THC directly in the PFC caused strong inhibition of VTA DA neuronal activity states and a corresponding blunting of emotional memory processing. These data provide a neurobiological mechanism by which cannabinoids can functionally regulate emotional salience processing through prefrontal-cortical to mesolimbic pathways.[42]

Adolescent THC alters behavioral, synaptic, and molecular phenotypes in the adult brain

In rats, the neurobehavioral features of adolescence are observed from approximately postnatal days (PND) 28–42, with early changes occurring at PND 20 in females and ongoing until PND 55 days in males.[1] Rats exposed to THC at the onset of puberty display decreased social play in adolescence, showing that the negative effects of cannabis appear quickly in developing rodents.[43]

Various rodent studies have examined the effects of adolescent exposure to THC during specific windows of vulnerability to assess the impact on neurodevelopmental processes. While these studies have used a variety of THC exposure protocols and time frames, several consistent phenotypes have emerged.

One such consistent protocol has been adolescent exposure of female and male rats to increasing doses of THC for 11 days (PND 35–45) before an abstinence period until adulthood (PND 75) to perform an array of behavioral, electrophysiological, and biochemical assays.[44] Therein, the authors did not observe changes in anxiety-related behaviors, however, both female and male rats displayed evidence of anhedonia phenotypes.

Using an identical THC exposure protocol, Renard et al[45] reported that adolescent THC induced strong anxiety- and depression-like phenotypes as well as deficits in social cognition and memory in male rats. In female rats, depressive-like behaviors were observed in response to THC and the synthetic agonists CP55,940 and WIN55,212-2 (WIN) but curiously not HU-210, suggesting that not all cannabinoid receptor agonists may induce long-term negative effects.[46] While adolescent THC exposure did not significantly alter adult sensitivity to non-noxious or noxious stimuli, or the antinociceptive effect of THC, it altered adult exploratory and consummatory behaviors in a sex-dependent manner: adolescent THC reduced hedonic drinking in adult males, and THC-induced hedonic drinking in adult females.[47]

These behavioral phenotypes corresponded to a persistent subcortical hyperdopaminergic state characterized by significantly potentiated firing frequency and

bursting rates in subpopulations of VTA DA neurons observed during *in vivo* single unit recordings.[45]

Furthermore, THC-exposed animals exhibited several schizophrenia-like molecular adaptations in the PFC (e.g., glycogen synthase kinase-3, protein kinase B, and mammalian target of rapamycin-signaling pathways) that persisted into adulthood. These effects were entirely absent in control rats that received THC exposure only after reaching adulthood, underscoring the exquisite vulnerability of the adolescent brain to extrinsic insults from THC. These cortical molecular biomarkers are critically involved in cognitive processing and are linked to the cognitive deficits associated with various neurodegenerative and neuropsychiatric disorders, including Alzheimer's, schizophrenia, and major depressive disorder,[48,49] suggesting that neurodevelopmental cannabinoid exposure may be capable of broadly impacting molecular signaling pathways that could increase risk factors for various neuropsychiatric disorders with underlying cognitive pathologies.

At the cortical level, a subsequent study using this protocol examined the effects of adolescent THC exposure on PFC neuronal activity states.[50] As above, the authors reported significantly increased firing rates and bursting activity in subpopulations of presumptive pyramidal neurons recorded directly in the rat PFC. Interestingly, cannabinoids have previously been reported to acutely increase the bursting states of PFC neurons, an effect that was associated with the ability of cannabinoids to pathologically amplify associative fear memory formation.[51,52] At the molecular level, alterations were noted in another critical schizophrenia-like biomarker following adolescent THC exposure: significant reductions in levels of GAD67 directly in the PFC, indicating a loss of cortical inhibitory control, consistent with evidence found in studies of schizophrenia patients.[53,54] Beyond reported changes in single unit neuronal activity within the mesocortical network, adolescent THC exposure has been shown to disrupt oscillatory activity patterns.

Specifically, adolescent THC exposure was reported to cause long-term elevations in gamma-band activity patterns within the PFC of rats,[50] highly consistent with clinical phenotypes showing abnormal gamma oscillatory band patterns in schizophrenia.[55,56] Finally, adolescent THC exposure-induced depressive behaviors have also been linked to a reduction in dorsal raphe serotonergic neural activity, identifying monoaminergic systems as prime targets of THC.[57]

Cannabinoid exposure alters the adolescent endocannabinoid system

The endocannabinoid (eCB) system (ECS) is dynamic both temporally and spatially throughout adolescence. Thus, recreational use of cannabinoids by adolescents is bound to manipulate the functions of naturally occurring eCBs and thereby impact eCB signaling molecules and functions. Upon repeated adolescent exposure to cannabinoids, long-lasting changes in the ECS are consistently reported. For example, the above-discussed study of adolescent THC exposure[44] found that CB1R expression and CB1R/G-protein coupling were significantly reduced by THC exposure in amygdala, VTA, and nucleus accumbens (NAc) of female rats at adulthood, whereas male rats were only affected in the amygdala and hippocampus. Further illustrating this idea, Leishman et al[58] found that acute treatment with the synthetic cannabinoid, CP55940, had stronger effects on the female mouse brain lipidome during adolescence than during other developmental stages.

CB1R expression is reduced in the PFC of WIN-treated female mice[59] and in the female hippocampus 2 weeks following adolescent THC treatment.[60] Repeated administration of the FAAH inhibitor, URB597 (which thusly increases AEA levels), during adolescence persistently decreased CB1R binding in the caudate–putamen, NAc, VTA, and hippocampus, and led to increased CB1R binding in the locus coeruleus.[61]

Molecular mechanisms underlying the lasting effects of adolescent cannabis exposure remain elusive. Nonetheless, current data indicate that the ECS, in addition to fast glutamatergic and GABAergic synapses, are the main targets. Early life and adolescence are well-described periods of changes for the ECS. Early data from de Fonseca et al described sex differences in CB1R expression starting at early postnatal development and peaking around adolescence.[62,63]

Analysis in humans of the ontogenetic pattern of CB1R confirmed that its expression increases during the transition from adolescence to adulthood, a rare feature during adolescence.[64] Such developmental changes in CB1R occur in parallel with fluctuations of the circulating levels of anandamide and 2-arachidonoylglycerol (2-AG), which themselves peak during adolescence.[65–68] Reports of increased CB1R messenger RNA (mRNA) expression in the central amygdala[60] and of increased CB1R binding in the locus coeruleus[61] indicate a degree of regional specificity in the protracted consequences of cannabinoid exposure on the main receptor target of exogenous cannabinoids.

Adolescent cannabinoid exposure alters dendritic architecture

Dendritic specializations, especially synapse-bearing spines, are the communicating interface between most neurons. Dendritic communication integrates synaptic inputs, neuromodulatory influences, and neuronal passive properties to fine tune and otherwise modulate the genesis of action potentials. Thus, dendrites are essential to neuronal and circuit computation and therefore to resultant cognitive processes. Adolescence is a period of profound sex-dependent neuronal maturation. Dendritic complexity, as well as spine shape and number, are subject to intense remodeling during adolescence, particularly in brain areas involved in the highest cognitive functions such as the PFC. During sensitive periods such as adolescence, experiences can greatly alter the appearance types and longevity of dendritic spines and that these effects can be sex specific.[69–72] Thus, environmental influences, including consumption of drugs of abuse such as cannabis and related risk-taking behaviors, may all have profound impact on crucial developmental processes during this maturational window.

While CB1R are largely absent from dendrites (except for early developmental stages[73]), other receptor components of the ECS are present and cannabinoids, by virtue of their multiple receptor and downstream targets expressed on all neuronal subdivisions, can change spines' shape and dendrites' arborization/architecture.

First reported in adults,[74] the transformative power of THC was originally elucidated by Rubino et al in their pioneering 2009 study.[75] Therein, adolescent THC exposure (PND 35–45) reduced dendritic length, as well as the number and density of spines in hippocampal granule cells of the dentate gyrus in adult rats 1 month after the last injection. Similar results have been observed in the PFC following chronic adolescent exposure to THC.[76] Behaviorally, the resultant THC-exposure "dendritic phenotype" originally described by Rubino and colleagues was associated with poor performance in assays of memory (e.g., radial arm maze acquisition time) and increased psychotic-like behaviors in male rats without alterations in the emotional reactivity (e.g., passive avoidance test[77]).

When female adolescent rats were similarly exposed to THC, a reduction of dendritic spine density was observed in the adult PFC together with deficits in both cognitive and emotional behavioral domains.[44,69] In both sexes, the structural modifications were paralleled by multiple changes of the synaptic repertoire of NMDA- and AMPA-type glutamate receptors in addition to other essential molecular constituents of excitatory[76,78,79] and inhibitory synapses.[80] Notably, a recent study shows that adolescent THC engagement differentially impacts synaptic organization in the prelimbic PFC by increasing muscarinic-2 receptors (M2R) plasmalemmal accumulation in large proximal dendrites and decreasing M2R cytoplasmic expression in small spines.[81] Furthermore, transcriptomic data suggest that adolescent exposure to THC alters the transcriptional trajectory and dendritic architecture of prefrontal pyramidal neurons by acting on functional gene networks linked to cell morphogenesis, dendritic development, and cytoskeleton organization.[82]

Altogether, these data provide a structural foundation to the long-lasting sex-specific cognitive deficits resultant of chronic, but not acute,[83] adolescent cannabinoid exposure.

Adolescent cannabinoid exposure alters neuronal and synaptic properties

In mammals, activity-dependent changes in the efficacy of synaptic transmission are central to the development of neural circuitry and functions of memory, including the storage of information and behavioral adaptations. Thus, synaptic plasticity is one of the neurobiological foundations of higher cognitive function. At the structural and molecular levels of synaptic function, cannabinoid-induced changes in dendrites and spines are bound to impact how information flows from synapses to cell bodies and therefore synaptic transmission and plasticity. Evidence of lasting modifications to synaptic transmission and plasticity following various regimens of exposure to cannabinoids during adolescence is abundant.[40,50,76,84]

eCB-mediated retrograde signaling equips most central synapses bearing CB1R and/or TRPV1R with a robust means of activity-dependent plasticity (e.g., LTD[85,86]), which has been the subject of substantial investigations into the acute and protracted effects of cannabinoids on forms of plasticity such as eCB-LTD in the adult brain.[87,88] Curiously, how adolescent cannabis can interfere with eCB-mediated and eCB-independent synaptic functions and/or synaptic plasticity is a relatively new and underrepresented field of study.

The existence of sensitive periods within the period of adolescence itself was first suggested by the study of Cass et al who reported that WIN exposure during early and mid but not late adolescence, reduced GABAergic inhibition in the PFC and caused prefrontal

disinhibition in adulthood.[89] However, earlier data from Abush and Akirav demonstrated that chronic intraperitoneal (i.p.) treatment of male rats with the synthetic cannabimimetic WIN during late adolescence (PND 45–60) hampered LTP in the ventral subiculum accumbens pathway up to 10 days after withdrawal while cognitive deficits in a hippocampal-dependent task lasted up to 75 days.[90] WIN exposure during early adolescence suppresses oscillations not only in the adult medial PFC but also the somatosensory cortex.[91] As in other studies, this lasting disruption is attributed both to CBR-dependent and independent mechanisms.

Two recent reports identified the extracellular matrix glycoprotein reelin as a potential mediator of the behavioral, dendritic, and synaptic deficits following adolescent mice exposure to cannabinoids.[92,93] Normally involved in cortical development (notably that of the PFC[94]) reelin is also a risk factor in psychiatric disorders and taken these findings illustrate how adolescent cannabinoid exposure interacts with other risk factors in schizophrenia.[95]

In the search for synaptic substrates underlying the deleterious consequences of cannabinoid exposure during adolescence on female behavior and dendrites,[44,75,77,96] several groups concomitantly found that prefrontal LTP[76] and LTD mediated by metabotropic glutamate receptors 2/3 (mGluR2/3[85]) or eCB[97] were deficient in adulthood in mice treated with natural or synthetic cannabinoids.[44,59] Furthermore, Rubino et al showed that, following the manifestation of these lasting deficits, pharmacological enhancement of levels of the eCBs 2-AG or anandamide levels through blockade of their principal degrading enzyme restores eCB-LTD.[44,98] Similar restoration of plasticity deficits has been demonstrated in mouse models of autism and depression.[84,99,100] In the case of adolescent cannabinoids, it is not known if the pharmacomodulation of eCB levels also rescue behaviors.

The long-term consequences of teenage cannabis use extend beyond cortical areas. For example, 7–10 days of THC exposure abolished eCB-LTD at glutamatergic inputs to VTA GABA cells of juvenile–adolescent-age mice.[101] Further studies are required to determine the relationship between the latter finding and the observation that WIN is more efficacious at triggering striatal Dopamine release during adolescence compared with adulthood.[102] As above, these data highlight the nature of developmental fluctuations in expression of ECS components during development, which confer specific windows of developmental vulnerability.

Despite the apparent value of single-exposure studies to elucidating the consequential neuroadaptations in response to initiation of cannabis use, the acute effects of adolescent cannabis exposure have received minimal preclinical attention. Results to date indicate that a single THC exposure ablated eCB-LTD in the PFC of females (while males were spared), but had no effect on PFC-LTP (in both sexes) nor eCB-LTD at the glutamatergic inputs to VTA GABA cells in male mouse.[101,103] Altogether these data indicate that adolescent cannabis exposure profoundly impacts synaptic plasticity in a region-, sex-, and time-dependent manner. This interpretation, not surprising given the sensitive and fluid nature of adolescent neurodevelopment, provides strong incentive for a more systematic evaluation of the acute and protracted consequences of acute (single) or repeated cannabinoid exposure in both sexes.

Zhang et al first reported region- and age-specific differences in the ability of endogenous and exogenous cannabinoids to induce LTD in the striatal complex of male mice[104] and recent evidence indicates that the developmental course of eCB-LTD in PFC is sexually dimorphic.[105] eCB-LTD first appears during the juvenile period in female rats, while emerging during puberty in males. Strikingly, eCB-LTD is mediated by distinct receptors in males and females dependent on their developmental stage. Female rats use both CB1R and TRPV1R for the induction and maintenance of eCB-LTD during the juvenile stage, but only CB1R at puberty, and only TRPV1R at adulthood. In contrast, eCB-LTD is exclusively mediated by CB1R in both pubescent and adult males.

The existence of distinct maturational pathways in male and female brains implies that the acute and lasting effects of exogenous cannabinoids depend not only on sex, but also on the developmental state of the ECS at the stage of exposure.

Current knowledge favors the hypothesis that additional cellular substrates for sex-specific behavioral and synaptic abnormalities caused by adolescent exposure to cannabinoids include modifications of the synaptic repertoire of glutamatergic and GABAergic synapses. Illustrating this, adolescent cannabinoid exposure differentially impacts multiple components of synaptic machinery in the PFC: CB1R and mGluR2/3 expression is reduced in WIN-treated female mice[59]; PFC GABAergic transmission is functionally downregulated after adolescent WIN exposure[89]; and cannabinoid exposure-induced enhanced PFC expression of

the scaffolding protein PSD-95 is paralleled by increased expression of GluN1,[79] GluN2A/B, and GluA1 subunits.[69] Finally, data indicate that adolescence cannabis exposure results in a persistent neuroinflammatory state located in the adult PFC,[77] leading to a diverse set of behavioral consequences owing to the PFC's role as a neurocognitive hub or relay.

While Δ9-THC is the component of most concern in *Cannabis sativa* with regard to adolescent health, the plant contains over 300 compounds, including CBD. CBD does not induce psychotropic effects compared with Δ9-THC[106,107] and, as such, it is globally perceived as safe and free of harmful side effects. Additionally, authorization of CBD by several health-governing bodies globally indicates an acceptable level of safety for use in necessary conditions such as intractable seizure disorders. Nonetheless, data on the impact of CBD on the developing brain remains relegated to the pre-clinical body of literature, and despite this paucity of data on the impact of CBD on the adolescent brain and body, its therapeutic and recreational use is growing.[108]

Administration of CBD for 2 weeks (5, 10, or 30 mg/kg; i.p.) to juvenile rats (PND 30) has been found to significantly disrupt metabolic markers and the sleep–wake cycle in young adult rats (PND 80). Increased blood glucose and decreased plasma triglyceride levels in adipose and hepatic tissue indicate disrupted metabolic activity in one study[109] in contrast with another report.[110] Interestingly, female weight gain is reduced during adolescent exposure to CBD.[111] In adult rats exposed to CBD during adolescence (5 or 30 mg/kg, i.p.; PND 30–44), arousal, rapid eye movements (REM), and slow sleep are disrupted and NeuN expression increased in the suprachiasmatic nucleus.[112] Interestingly, similar alterations of REM, wakefulness, and NeuN expression have been reported in response to an adolescent exposed to a synthetic cannabimetic.[113]

Multiple aspect of emotional regulation and cognition are sensitive to CBD exposure during puberty. In late adolescence (PND 45), single administration of CBD has antidepressant-like effects in unstressed Swiss mice in the tail suspension and elevated plus maze (EPM) tests.[114] C57BL/6J mice of both sexes repeatedly exposed to CBD during adolescence showed reduced anxiety in the EPM and improved learning in a spatial memory task at PND 60.[115] Social interaction and freezing in response to contextual fear conditioning were both augmented up to 30 days postadolescent CBD treatment.[111] While in adolescent male rats, CBD ameliorates behavioral despair in the forced-swim test, CBD does not modulate anxiety-like behavior or sucrose preference in mice,[112] suggesting species differences.

In female rats, CBD attenuates some long-term behavioral alterations induced by adolescent THC exposure and prolonged changes in prefrontal CB1R and microglia activation. In addition, chronic administration of CBD-rich cannabis with a CBD:THC ratio analogous to that found commercially, negatively affects cognition, results in anhedonia, and alters prefrontal GABAergic neurotransmission when administered during adolescence in female rats (PND 35–45[116]). In mice, coadministration of CBD confers protection against all THC-induced behavioral abnormalities in adolescents, but unlike in rats, CBD alone has no behavioral effects.[117]

Although still rare and partly contradictory due to species and treatment differences, the available evidence suggests a complex situation. The fact that CBD in adolescence affects multiple aspects of cognition in a sustained manner prompts a cautious approach.

Overall, the data concerning cannabis exposure during critical periods of development have highlighted the labile and sensitive nature of neuronal programming schema and the crucial role of the ECS in guiding and modulating these processes. In this study, research detailing the impact of exogenous cannabinoid exposure at various stages of development have been detailed and revealed a consistent theme: developmental organization principles and functional outcomes, ranging from synaptic plasticity to complex behaviors, are profoundly impacted through cascading insult from early-life exocannabinoid interference. Thus, developmental windows wherein principal neuronal guidance is affected or governed by the ECS, from early prenatal life through adolescence and early adulthood, require careful consideration with regard to exocannabinoid exposure.

Concluding Remarks

Overall, the data concerning cannabis exposure during critical periods of development have highlighted the labile and sensitive nature of neuronal programming schema and the crucial role of the ECS in guiding and modulating these processes. In this study, research detailing the impact of exogenous cannabinoid exposure at various stages of development have been detailed and revealed a consistent theme: developmental organization principles and functional outcomes, ranging from

synaptic plasticity to complex behaviors, are profoundly impacted through cascading insult from early-life exocannabinoid interference. Thus, developmental windows wherein principal neuronal guidance is affected or governed by the ECS, from early prenatal life through adolescence and early adulthood, require careful consideration with regard to exocannabinoid exposure.

Future Research Directions, Pressing Questions

One of the most pressing limitations related to our understanding of the effects of adolescent cannabis exposure on vulnerable brain development periods is that most of the extant literature examining these effects have relied primarily on systemic injections of purified THC extracts or synthetic cannabinoids. Given the primary route of cannabis consumption is through smoked or vaped inhalation and/or edible formats, this might raise concerns about potential differences in cannabinoid metabolism, distribution, and pharmacokinetics between systemic versus inhaled/edible cannabinoid exposure routes and translational validity of pre-clinical models.

Nevertheless, previous studies using direct comparisons between inhaled versus intravenous routes of THC exposure have observed similar levels of THC in both blood and brain,[118,119] demonstrating the validity of systemic THC injection protocols to accurately mimic THC exposure. Beyond the issue of administration route, cannabis is known to contain over 100 distinct phytochemical constituents. There is, therefore, an urgent need to better understand how exposure to combinations of cannabis-derived phytochemicals (including the lesser cannabinoids such as cannabigerol, cannabichromene, and the monoterpenes) might act synergistically to increase neuropsychiatric risk.

In addition, while many studies reviewed in this article have examined the effects of direct THC exposure during adolescent brain development on sequelae associated with neuropsychiatric phenotypes, less is known regarding how exposure to cannabinoids during adolescence might interact with specific environmental factors to increase disease risk or render the brain more sensitized to exposure to environmental risk factors such as acute or chronic stressors.

Outstanding Questions

(1) How might long-term neuronal phenotypes associated with adolescent THC exposure, such as hyperactive subcortical DA or cortical activity states, increase brain vulnerability to subsequent environmental stressors, consistent with a "two-hit" hypothesis of the etiology of disorders like schizophrenia?
(2) Is the influence of endogenous and exogenous cannabinoids in adolescence different than in other periods of development? Does adolescent cannabis change the course of the "endogenous cannabinoid program" normally engaged across the lifespan, including aging? How do these impacts compare to gestational exocannabinoid exposure and adulthood cannabinoid consumption?
(3) What are the functions and molecular mechanisms of the endogenous cannabinoid system/program in adolescence? Are they the same as in early childhood and adulthood? What is the role of puberty and sex in the onset of the cannabinoid-sensitive period in adolescence?
(4) Is the timing and duration of the "adolescent cannabinoid-sensitive period" aligned with that of the adolescent sensitive period? What is the role of sexual and individual differences in determining the onset and duration of the "cannabinoid-sensitive period" during this time of life?
(5) How do environmental influences such as infectious and/or genetic diseases, stress, or drug (legal and illegal) use impact the functions of endocannabinoids in brain development in humans?
(6) Are the effects of adolescent cannabis exposure reversible? Can we exploit the adolescent cannabinoid-sensitive period for remedial interventions? If so, what are the side effects of such interventions? What are the ethical implications of cognitive alteration through cannabinoid modulation?

Authors' Contributions

A.F.S.: Conceptualization and writing—original draft, review, and editing. A.-L.P.: Conceptualization, funding acquisition, and writing. S.R.L.: Conceptualization, funding acquisition, and writing. O.J.J.M.: Conceptualization, funding acquisition, and writing—original draft, review, and editing.

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Abbreviations Used

2-AG = 2-arachidonoylglycerol
CBD = cannabidiol
ECS = eCB system
EPM = elevated plus maze
INSERM = Institut National de la Santé et de la Recherche Médicale
i.p. = intraperitoneal
LTD = long-term depression
LTP = long-term potentiation
M2R = muscarinic-2 receptors
mGluR2/3 = metabotropic glutamate receptors 2/3
NAc = nucleus accumbens
PFC = prefrontal cortex
PND = postnatal days
REM = rapid eye movements
THC = tetrahydrocannabinol
VTA = ventral tegmental area
WIN = WIN55,212-2