

## EXPERT REVIEW

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# Cannabinoid CB1 receptor-sensitive neurodevelopmental processes and trajectories

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As high-potency cannabis (with high Δ<sup>9</sup>-Tetrahydrocannabinol content) becomes easily accessible and widespread, it is of extreme importance for public health that a scientific platform is used to implement practical guidelines, particularly for at-risk populations. Many reviews have been written in the past decade summarizing the impact of cannabis in the developing brain. One critical concept frequently mentioned but not discussed in detail is whether there are sensitive neurodevelopmental events driving the age-specific sensitivity to cannabis, particularly those mediated by cannabinoid type 1 receptor signaling. By integrating available data from humans and animal models, the goal of the present expert review article is to provide a mechanistic overview on how cannabis exposure during sensitive periods of neural circuit plasticity and development can result in lasting consequences. Here we used the frontal cortex as a proxy to align the trajectory of the brain cannabinoid system between humans and rodents. Both the strengths and limitations of available mechanistic studies on the effects of cannabis and cannabinoids were discussed using a developmental framework from which neural circuit adaptations during sensitive periods are considered. Such an approach is needed to align key neurodevelopmental variables through the lifespan, which in turn will provide valuable insights applicable to the human brain by defining the underpinning mechanisms of sensitive periods and how the impact of cannabis changes from childhood to adolescence, and thereafter through young adulthood.

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## INTRODUCTION

The terms cannabis and marijuana are often used interchangeably despite that they are technically distinct. While "cannabis" is used for all extracts derived from the cannabis plant, "marijuana" specifically refers to products made from *Cannabis sativa*'s or *Cannabis indica*'s dried leaves, flowers, stems and seeds (<https://nida.nih.gov/research-topics/cannabis-marijuana>) containing the psychoactive chemical Δ<sup>9</sup>-Tetrahydrocannabinol (Δ<sup>9</sup>-THC) [1]. According to the National Institute on Drug Abuse (NIDA), the **average** amount of Δ<sup>9</sup>-THC found in cannabis/marijuana seized by the DEA from 1995–2022 increased from 4–16% (<https://nida.nih.gov/research/research-data-measures-resources/cannabis-potency-data>). Currently, the amount of Δ<sup>9</sup>-THC found in marijuana can be as high as 40% or more, with low concentrations defined as <10%, and high concentrations as >15% (<https://nida.nih.gov/research-topics/cannabis-marijuana#cannabis-getting-stronger>). In addition to Δ<sup>9</sup>-THC, there are more than one hundred cannabinoid constituents or phytocannabinoids that have been identified in the cannabis plant and classified into 11 types [2, 3]. Regardless of the term used to refer cannabis-derived products, a major challenge today is the application of sensitive research strategies to identify mechanisms by which the different types of cannabinoids impact neuronal activity and brain function through the lifespan.

According to the National Institute on Drug Abuse (NIDA) "Marijuana Research Findings: 1976" report, marijuana use among adolescents (12–17 years old) and young adults (18–25 years old)

began to increase in the USA during the 1960's. One of the main conclusions of the 1976 report stated that "*marijuana is most widely used by adolescents and young adults during sensitive stages in their personality development, while developing intellectual and psychosocial skills*", and "*To what extent, if any, chronic intoxication affects development is still unknown*" (NIDA research monograph 14, 1976). This concern continues today as the maturation of executive functions such as working memory, decision making, and inhibitory control needed for the acquisition of adult behavior take place during the transitional period of adolescence [4–8]. Furthermore, there is converging evidence supporting the notion that early-onset cannabis use could increase the incidence of developing cognitive-associated psychiatric syndromes and substance use disorders later in life [9–17]. Certainly, establishing a causal link between cannabis use (e.g., frequency, age of onset, Δ<sup>9</sup>-THC content, route of administration) and the onset of mental illnesses remains a major challenge (see [18]). However, as high-potency cannabis (high Δ<sup>9</sup>-THC content) becomes easily accessible, it is extremely important for public health that well-designed mechanistic studies are used to establish a scientific platform for the implementation of practical policy and guidelines, especially for at-risk populations.

Numerous expert reviews and commentaries have been written in the past two decades on neurobiological consequences resulting from the developmental impact of Δ<sup>9</sup>-THC and the potential underlying mechanisms [19–30]. However, one critical concept that is often mentioned but not discussed in detail is the

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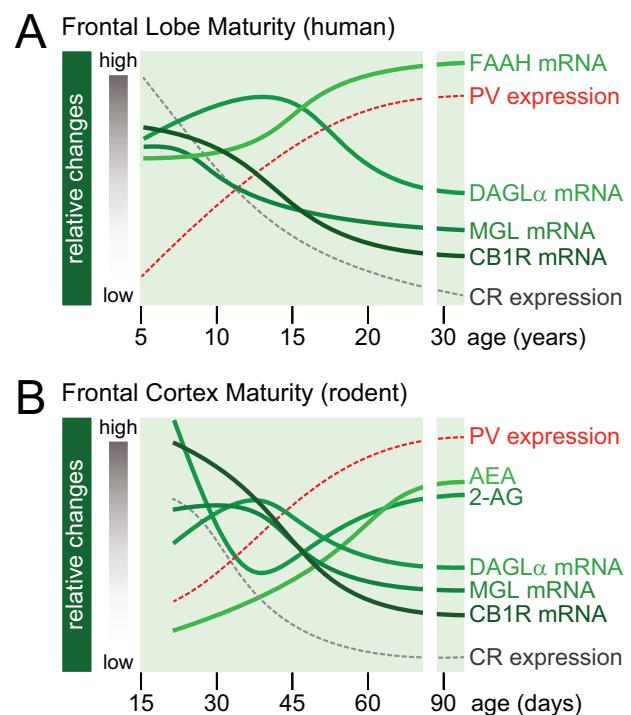
extent to which sensitive neurodevelopmental processes contribute to the age-specific vulnerability to  $\Delta^9$ -THC. Thus, the goal of the present review article is to provide a mechanistic overview focusing on cannabis-sensitive periods of neural circuit plasticity and development, particularly those processes that are sensitive to  $\Delta^9$ -THC and cannabinoid type 1 receptor (CB1R) signaling, which are linked to the detrimental impact of cannabis. We will use the frontal cortex as a proxy to integrate available data of the brain endocannabinoid system and match the most conserved developmental variables [31] to align the trajectories between humans and rodents. We will then elaborate and discuss the possibility that fluctuations in the trajectories of pre- and postsynaptic adaptations during the development and maturation of distinct neural circuits could dictate the length of a sensitive period and its end. Finally, we will highlight both the strengths and limitations of available mechanistic studies aimed at elucidating the neurobiology underlying the developmental impact of cannabis/cannabinoids by integrating the major findings obtained from rodents and humans.

## DEVELOPMENTAL TRAJECTORIES OF THE BRAIN ENDOCANNABINOID SYSTEM

It is well established that the different effects of  $\Delta^9$ -THC on neuronal function and behavior are mediated by the activation of the CB1R and associated postsynaptic signaling events [32–35] including those observed in human subjects [36–39]. In fact, treatment with the CB1R antagonist rimonabant can effectively attenuate major behavioral changes resulting from  $\Delta^9$ -THC exposure such as altered perception and distractibility, working memory deficits and increased anxiety and euphoria [36, 38]. As one of the most abundant G-protein coupled receptors in the brain [40–42], stimulation of CB1R with exogenous ligands is expected to alter the balance of excitatory and inhibitory synaptic activity [43, 44] and its control of neural circuit plasticity and behavioral responses [45, 46]. It is therefore conceivable that the neural mechanisms underlying the age-dependent susceptibility to cannabis are modulated by the developmental trajectory of the brain endocannabinoid system including the expression of CB1R.

A key challenge in developmental neuroscience is the integration of neurobiological variables across species with different lifespans. By using two conserved markers of cortical interneurons and the frontal cortex [31], we projected that a 5-day developmental window in rodents would be equivalent to 3 years in humans as estimated by the concurrent opposing changes of calretinin (CR) and parvalbumin (PV) expression between 12 and 20 years of age in humans and postnatal days (P) 35 and 55 in rats (Fig. 1). Through this approach and by integrating available data from the human and rodent frontal cortex, we were able to align the distinct trajectories of the brain endocannabinoid components from childhood to young adulthood and equivalent postnatal days in rats (Fig. 1A, B).

Specifically, CB1R expression in the frontal cortex is highest at the onset of adolescence and begins to decline thereafter through young adulthood in both humans [47, 48] and rodents [49]. A similar trajectory was observed with the level of diacylglycerol lipase- $\alpha$  (DAGL $\alpha$ ) and monoacylglycerol lipase (MGL) [48, 50], which are the synthesizing and degrading enzymes for the CB1R endogenous ligand 2-arachidonoylglycerol (2-AG), respectively. Interestingly, the patterns of DAGL $\alpha$  and MGL do not match with the trajectory of 2-AG levels based on available data from the rodent prefrontal cortex (Fig. 1B). Contrary to the level of the other endocannabinoid anandamide (N-arachidonylethanolamine or AEA) that steadily increases through adolescence onto young adulthood [51], 2-AG levels follow a non-linear pattern [51], which is characterized by a major drop from the onset of adolescence and a steady increase thereafter to match the trajectory of AEA (Fig. 1B). Finally, data from human samples [48] suggests that the trajectory for the fatty acid



**Fig. 1 Comparative developmental trajectories of the brain endocannabinoid system: human vs. rodent frontal cortex [47–51].** **A** Summary of neurobiological variables measured in human postmortem studies. The patterns of parvalbumin (PV) and calretinin (CR) mRNA expression (Caballero and Tseng, [31]) were included to align the trajectories of the different endocannabinoid components observed in the human frontal cortex with those found in rodents [47–51]. **B** Using this developmental framework, a 5-day window in rats would be equivalent to 3 years in humans [31]. A major shift in the trajectories of the rodent frontal cortex endocannabinoid system emerges between postnatal days (P) 30 and 60 [47–51]. Note that the human frontal cortex experiences similar patterns of changes within the 10–20 years of age period. AEA N-arachidonylethanolamine or anandamide, CB1R cannabinoid type 1 receptor, CR calretinin, DAGL $\alpha$  diacylglycerol lipase- $\alpha$ , MGL monoacylglycerol lipase, PV parvalbumin, 2-AG 2-arachidonoylglycerol.

amide hydrolase (FAAH) enzyme, which breaks down AEA, is opposite to those of DAGL $\alpha$  and MGL (Fig. 1A).

Future studies are needed to fill the developmental gaps in rodents (e.g., FAAH mRNA) and humans (e.g., 2-AG and AEA levels) and expand the current analyses to other brain regions. However, it becomes clear from the integration of available data through the lifespan that the distinct trajectories within the brain endocannabinoid system are conserved between humans and rodents (Fig. 1). This approach is expected to provide valuable insights applicable to humans by defining the mechanisms of sensitive periods and how the impact of cannabis on CB1R signaling and neural circuit plasticity changes from childhood and adolescence to adulthood [19, 52].

## CB1 RECEPTOR-SENSITIVE DEVELOPMENTAL PERIODS AND THE MATURATION OF CORTICOLIMBIC CIRCUITS

The recruitment of the brain endocannabinoid system is typically activity-dependent and utilizes a CB1R-mediated retrograde signaling to limit the gain of GABA and glutamate transmission [43, 44, 53, 54]. Due to the prevalence of the CB1R throughout the brain [49, 55] and its role on synaptic plasticity [53], it is conceivable that the neurobiology contributing to the age-dependent effects of cannabis and  $\Delta^9$ -THC is mechanistically

linked to neural processes underlying the development of sensitive periods and neural circuit maturation [19, 52].

Different forms of activity-dependent plasticity (e.g., Hebbian) and homeostatic adaptations are needed at both excitatory and inhibitory synapses during the formation and maturation of neural circuits which occurs through a series of developmental stages that are sensitive to environmental factors, often referred as “critical” periods (see [56]). Hence, exposure to  $\Delta^9$ -THC is expected to trigger distinct maladaptive trajectories of brain development depending on the sensitive period and the underlying mechanisms driving neural circuit maturation at that stage. This developmental framework is certainly applicable to other types of drugs and environmental stimuli (e.g., stressors) and to delineate potential mechanisms by which a sensitive period ends.

### Cannabis exposure during the pre/perinatal period

The endocannabinoid system through the CB1R signaling is known to play a critical role in shaping the formation of neural circuit connectivity by modulating key neurodevelopmental events such as neuronal migration and proliferation, axonal growth and long-range axonal patterning [57–60]. As the formation of neural circuits begins, it is not surprising that pre/perinatal exposure to cannabis/cannabinoids results in lasting developmental dysregulation of synaptic function [61–68] that ultimately could lead to aberrant behavioral responses later in life, often within the cognitive and affective domains (see review by [21]). However, it remains unclear if all neurodevelopmental processes occurring during the entire prenatal-perinatal period are equally sensitive to cannabis regardless of the stage of development [69] and if the frequency of exposure and  $\Delta^9$ -THC content matters in conferring such susceptibility.

In human studies, converging evidence indicates that prenatal cannabis exposure can result in developmental delays in infants during the first 2 years of life [70]. Another observation with pre/perinatal cannabis exposure is the development of mental health problems that become apparent in early adolescence [71]. These findings suggest that an early life impact by cannabis could trigger a series of synaptic and neuronal maladaptive responses that will not emerge/become apparent until adolescence when the maturation of prefrontal-corticolimbic circuits [52] to support cognitive abilities associated with adult behavior occurs [5, 72]. A protracted onset of behavioral phenotypes following early developmental insults is not unique to cannabis, but a common phenomenon often linked to altered prefrontal circuit maturation and its meso-corticolimbic functional connectivity [73]. Supporting this hypothesis are recent studies from rodent models showing lasting behavioral changes following pre/perinatal cannabis exposure that can be attributed to a developmental disruption of the meso-corticolimbic system [61, 63, 74–77]. In fact, the mesolimbic circuit becomes disinhibited following prenatal and early postnatal  $\Delta^9$ -THC exposure, a developmental dysregulation affecting primarily male offspring [61, 76, 77]. Both plasticity at GABA and glutamatergic synapses modulating mesolimbic dopamine neurons are thought to contribute to the sex-related disruption [61, 76, 77]. Yet, the precise mechanisms driving such maladaptive developmental dysregulation remains elusive. Nevertheless, these findings reveal that early developmental exposure to  $\Delta^9$ -THC can lead to exaggerated mesolimbic dopamine responses that could lead to the development of addiction-like phenotypes, particularly within the male population [76, 78] and during sensitive windows of brain maturation such as adolescence.

Several molecular and epigenetic changes have been extensively discussed in the context of potential mechanisms driving the negative impact of cannabis exposure during prenatal and perinatal periods (e.g., [21, 23]). Of particular interest are preclinical studies in rodents showing that prenatal  $\Delta^9$ -THC exposure alters mRNA expression of the opioid peptide,

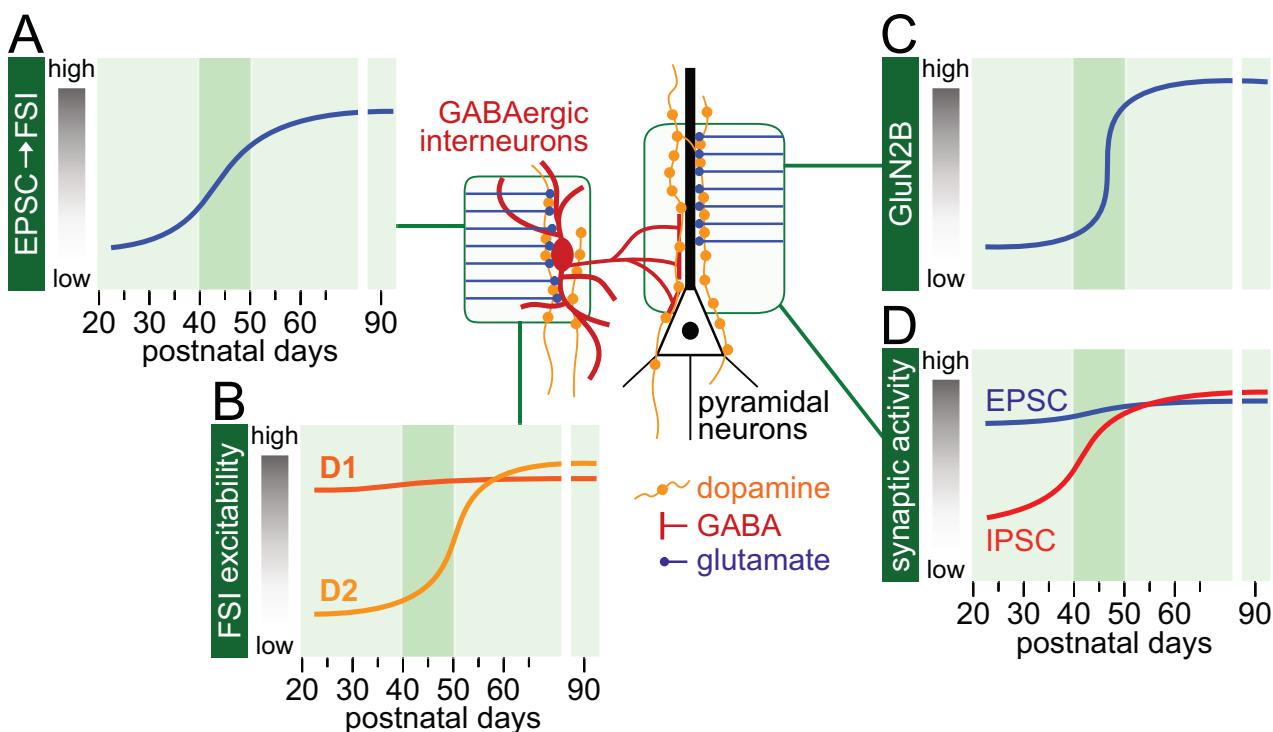
proenkephalin [66], and reduces dopamine D2 receptor gene expression within the mesolimbic circuit through histone modifications [79]. These epigenetic alterations could be mechanistically linked to the disinhibited mesolimbic circuit state found in offspring exposed to  $\Delta^9$ -THC during prenatal and early postnatal development [76, 78] and the development of addiction-like phenotypes later in life. However, only a few studies have included aspects of developmental trajectory in the experimental design to reveal age-sensitive maladaptive processes underlying the neurobiological effect of cannabis at early life [61–64]. Certainly, studies aimed at identifying the mechanisms driving the normal developmental trajectory of key neurobiological variables are crucial to gain insights on how distinct neural circuits adapt and become vulnerable to early life insults, and the extent to which maladaptive events last through the life span.

### Developmental trajectories of sensitive neurobiological processes during adolescence

It is well established that functional remodeling of key corticolimbic circuits continues through the sensitive period of adolescence [52] when the refinement of adult cognitive abilities such as problem solving, abstract thinking, and working memory takes place [5, 7, 72]. Such window of active remodeling creates a developmental period of sensitivity for environmental stimuli and insults to shape or alter the normal trajectories of neural circuit function (Fig. 2). Furthermore, the consumption of cannabis as well as the use of other drugs are expected to be amplified by the inherent novelty-seeking nature and increased risk-taking behaviors of the adolescent brain [6, 7]. Thus, a mechanistic analysis of the contributing factors driving and modulating the maturation of the corticolimbic circuitry is needed for understanding the neurobiology mediating the susceptibility to cannabis exposure during adolescence.

From the neurobiology standpoint, adolescence is currently viewed as a sensitive period during which major functional remodeling of local excitatory and inhibitory synaptic activity occurs in the prefrontal cortex following a unique age-related trajectory that directly impacts corticolimbic function and plasticity [52]. One key developmental factor shaping the maturation of corticolimbic circuits includes the functional recruitment of prefrontal GABAergic activity by excitatory afferents and dopamine during adolescence (Fig. 2A, B) that ultimately enables input selectivity and inhibitory control for sustaining working memory [80]. Such gain of synaptic activity in the prefrontal cortex during adolescence is certainly sensitive to cannabis exposure as the impact of CB1R signaling on prefrontal plasticity and function is age-dependent [45, 46, 49]. In addition to the gain of GABAergic output (Fig. 2A, B), is the strengthening of the ventral hippocampal-prefrontal pathway by the acquisition of GluN2B transmission during late adolescence (Fig. 2C) that also provides a mechanism for dopamine D1R modulation of input-specific afferent drive [80, 81]. Therefore, any disruption that compromises the normal gain of GluN2B and/or GABAergic function in the prefrontal cortex during adolescence (Fig. 2C, D) will alter the maturation of corticolimbic circuits and its impact on behavior.

Cannabis exposure during adolescence is expected to alter the trajectory of cognitive maturation [82] and its emotional regulation [83, 84] as these behavioral processes are mediated by significant changes in brain connectivity within the corticolimbic circuits [85, 86] expressing high levels of CB1R [47, 48]. As discussed above, the ventral hippocampal-prefrontal connectivity is of particular interest because it undergoes functional remodeling during adolescence [52] and is required for proper integration of contextual information [87–89]. Recently, a longitudinal study from human subjects (8–32 years of age) revealed that the enhanced hippocampal-prefrontal functional connectivity at rest [90] can predict the maturity of cognitive abilities to problem



**Fig. 2 Developmental trajectories of prefrontal synaptic activity and dopamine modulation.** **A** Trajectory of glutamatergic synaptic activity onto prefrontal cortical fast-spiking interneurons (FSI) as revealed by the frequency of excitatory postsynaptic currents (EPSC) [162]. **B** Trajectories of dopamine D1 and D2 receptors' action onto FSI in the prefrontal cortex. Both D1 and D2 receptor stimulation resulted in facilitation of FSI excitability [163]. However, the D2 receptor effect begins to emerge after P45 [163, 164] through the acquisition of a non-canonical,  $\beta$ -arrestin-mediated action [165]. **C** Trajectory of the GluN2B-mediated facilitation of synaptic activity in the prefrontal cortex, which occurs primarily onto the apical dendrite of layer V pyramidal neurons [81]. **D** Distinct developmental trajectories of spontaneous excitatory and inhibitory synaptic activity onto prefrontal layer V pyramidal neurons (see [93]). The frequency of inhibitory postsynaptic currents typically increases sharply after P40-45, a pattern that coincides with the increased EPSC frequency onto FSI shown in A. NOTE: The dark green shaded area highlights the adolescent period during which a shift in the trajectory of PFC glutamate and GABA synaptic function occurs.

solving and future planning through adolescence [90, 91]. Such maturation of cognitive functions is thought to be mechanistically linked to neural processes underlying the re-calibration of the excitatory-inhibitory ratio that typically occurs in cortical circuits during adolescence both in humans [92] and rodents [93]. Notably, the underlying synaptic mechanisms driving the re-calibration of the excitatory-inhibitory balance in the prefrontal cortex are linked to the maturation of ventral hippocampal-prefrontal functional connectivity [94–98], which are all regions susceptible to transient disruption of CB1R signaling within discreet adolescent periods [45].

The formation of the corticolimbic system begins early in life and develops through childhood [56]. However, it is the gain of GABAergic function (Fig. 2A, B, D) together with the recruitment of GluN2B transmission in the prefrontal cortex (Fig. 2C) by ventral hippocampal inputs [81] that could explain the late adolescent maturation of cognitive and emotional regulation subserved by the different meso-corticolimbic circuits. Importantly, plasticity within these networks is also sensitive to the impact of CB1R signaling in an age-related manner [45, 46]. It is therefore crucial to distinguish the potential underlying mechanisms driving the distinct neural circuit susceptibility during adolescence compared to older age groups.

#### Consequences of cannabis exposure during adolescence

Studies using rodent models have provided important evidence on how exposure to  $\Delta^9$ -THC or synthetic cannabinoids during adolescence, particularly before P50, affects neuronal and synaptic activity within the meso-corticolimbic system (Table 1). For instance, exposure to  $\Delta^9$ -THC within the P35-45 period led to

inhibition of endocannabinoid-mediated long-term depression in the prefrontal cortex when assessed in adulthood [99, 100].  $\Delta^9$ -THC exposure during a similar developmental window (P28-43) also reduced neuronal excitability in the prelimbic prefrontal cortex and attenuated NMDAR-mediated responses [101], which are essential for strengthening excitatory inputs from limbic structures such as the ventral hippocampus [81, 102]. Further, repeated exposure to the CB1R agonist WIN between P35-40 and P47-52 suppressed oscillatory activity in the prefrontal cortex [35], which are known to be developmentally regulated and dependent on local NMDAR transmission and postsynaptic D1R signaling [103, 104]. Similarly,  $\Delta^9$ -THC exposure between P35-45 markedly attenuated the activity of pyramidal neurons in the hippocampus causing a shift in theta and beta oscillatory power across both the dorsal and ventral hippocampus [105]. Together, these findings provide a mechanistic framework for understanding how repeated  $\Delta^9$ -THC exposure during adolescence compromises information processing within the hippocampal-prefrontal network and the resulting deficits in higher-order cognitive function in adulthood.

Cannabis exposure during adolescence also impacts key neurotransmitter systems involved in mood and reward processing (Table 1).  $\Delta^9$ -THC exposure from P30-50 led to reduced activity of dorsal raphe neurons [106], which are part of the serotonergic system that plays a critical role in mood regulation. In addition,  $\Delta^9$ -THC exposure between P25-45 increased the activity of dopamine neurons in the ventral tegmental area, a region central to the brain's reward circuitry [107]. On the other hand, an opposite effect on dopamine activity was found following cannabinoid exposure between P35-38 [108, 109], further indicating that age and/or duration of exposure matters when

**Table 1.** Changes in neural activity and synaptic transmission following repeated cannabis/cannabinoid exposure during adolescence in rodents.

Changes in Neuronal and Synaptic Activity	Age	Drug	References
Inhibition of endocannabinoid-mediated LTD in the adult medial prefrontal cortex (layer 2/3)	P35-45	THC	Cuccurazzu et al. [99]
Lower firing rate and bursting activity of pyramidal neurons in the dorsal hippocampus; Higher theta power in the ventral hippocampus; Higher beta power in the dorsal hippocampus and lower beta power in the ventral hippocampus	P35-45	THC	De Felice et al. [105]
Reduced activity of dorsal raphe neurons in both aged groups.	P30-50, P50-70	THC	De Gregorio et al. [106]
Enhanced activity of dopamine neurons in the ventral tegmental area.	P25-58	THC	Kruse et al. [107]
Reduced excitability of prelimbic prefrontal cortex neurons; Attenuated depolarizing response of prelimbic prefrontal cortex neurons to NMDA.	P28-43	THC	Pickel et al. [101]
Reduced dopamine cell response to WIN in both groups.	P35-38, P56-59	WIN	Pistis et al. [108]
Suppression of oscillatory activities in the medial prefrontal cortex.	P35-40, P47-52	WIN	Raver and Keller [35]
Increased neuronal firing in the ventral tegmental area after adolescent exposure.	P35-45, P65-75	THC	Renard et al. [115]
Reduced neuronal firing in the dorsal raphe; Increased neuronal firing in the locus coeruleus.	P30-50	WIN	Rodriguez et al [62]
Impaired endocannabinoid-mediated LTD in the prefrontal cortex	P35-45	THC	Rubino et al. [100]
Decreased WIN-induced dopamine firing in the ventral tegmental area and reduced dopamine levels in nucleus accumbens.	P45-55	THC	Scherma et al. [109]
Frequency dependent disinhibition local field potentials in the prefrontal cortex; Reduced GABAergic transmission onto layer V pyramidal neurons of the prefrontal cortex.	P35-40, P40-45, P50-55, P75-80	WIN	Cass et al. [45]

GABA gamma-aminobutyric acid, LTD long-term depression, NMDA N-methyl-D-aspartate, P postnatal day.

considering the long-term impact of cannabis and cannabinoids on neural function.

Table 2 summarizes how adolescent cannabis/cannabinoid exposure can trigger a wide range of biochemical and structural adaptations in the brain. One of the notable changes includes protein expression within various neurotransmitter systems.  $\Delta^9$ -THC exposure during adolescence downregulated dopamine receptor D2 (drd2) and adenosine A2A receptor (adora2a) gene expression in the nucleus accumbens and hippocampus, impairing dopaminergic and adenosine signaling pathways [110]. Exposure to  $\Delta^9$ -THC also altered the expression of receptors within both the glutamatergic and GABAergic transmission system. In the dorsal hippocampus,  $\Delta^9$ -THC exposure reduced the expression of NMDAR subunits, while in the ventral hippocampus, it increased these subunits and mGluR2/3 levels, contributing to region-specific alterations [105]. In the prefrontal cortex,  $\Delta^9$ -THC exposure during adolescence downregulates the levels of GAD65 in the prefrontal cortex, an enzyme critical for GABA synthesis [111], and disrupted the excitatory-inhibitory signaling balance by reducing GABA-Cnr1 expression and increasing glutamatergic Cnr1+ cells [11]. Both cortical GABA and glutamatergic systems are also sensitive to synthetic cannabinoids like JWH-018 and WIN [112, 113]. For instance, JWH-018 exposure reduced GAD67 expression in the prefrontal cortex and weakened local perineuronal nets, which are thought to contribute to the long-term neurobiological and behavioral deficits [112]. Similarly, WIN exposure through a self-administration protocol (i.v.) during adolescence altered the expression of proteins regulating GABAergic and glutamatergic signaling in the prefrontal cortex [113]. However, these changes resulting from WIN self-administration were not correlated with behavioral impairments, which is likely due to the different (lower) doses of WIN received during self-administration to those typically used in experimenter-administered studies (see [113]). Together, these findings are consistent with an earlier functional study showing that prefrontal inhibitory transmission is sensitive to disruption by repeated WIN exposure during adolescence [45]. In addition, the frequency-dependent disinhibition and the reduced GABA transmission observed in the prefrontal cortex following

WIN exposure during adolescence were detected only when the treatment occurred prior to P50 [45]. Collectively, the data revealed that there are distinct windows of vulnerability through adolescence.

Adolescent cannabis/cannabinoid exposure also induces biochemical changes in key signaling pathways that regulate synaptic transmission and plasticity (Table 2). An early proteomic study [114] suggested that synaptic plasticity within the hippocampus is compromised after adolescent  $\Delta^9$ -THC treatment. In the prefrontal cortex, decreased phosphorylation of proteins such as GSK-3 $\alpha$ / $\beta$ , Akt, and mTOR were observed following adolescent  $\Delta^9$ -THC exposure, while an opposite effect was found when  $\Delta^9$ -THC was given in adulthood [115]. At the structural level, adolescent  $\Delta^9$ -THC exposure can lead to premature dendritic spine pruning and negatively impact the maturation of synaptic connectivity and plasticity [116]. Such structural changes are often linked to alterations in epigenetic adaptations and gene networks (Table 2), many of which are disrupted following  $\Delta^9$ -THC exposure during adolescence [117, 118].

As expected, the brain endocannabinoid system is also sensitive to long-term adolescent  $\Delta^9$ -THC exposure (Table 2). Major changes include anandamide and 2-AG levels [51, 100] and CB1R expression [51, 100, 107, 119, 120] and G-protein coupling [121] across different brain regions. Although several potential mechanisms may contribute to driving these alterations within the endocannabinoid system (see Section 2), it remains unclear whether the changes observed in CB1R expression and endocannabinoid levels following  $\Delta^9$ -THC exposure are strictly age-dependent. Finally, changes in pro- and anti-inflammatory markers were found in the prefrontal cortex following  $\Delta^9$ -THC exposure during adolescence [122], supporting the notion that non-neuronal signaling (e.g., astrocytes and glial cells) in the brain are likely to play a role in conferring the adolescent vulnerability to cannabis [123].

## CANNABIS USE AND ITS IMPACT ON BRAIN FUNCTION IN HUMANS

As the access to cannabis is steadily rising [124], a major concern is the increased liability of developing neuropsychiatric syndromes

**Table 2.** Biochemical and structural changes in brain following repeated cannabis/cannabinoid exposure during adolescence in rodents.

Biochemical and Structural Changes	Age	Drug	Citation
Increased kynurenic acid levels in the adult prefrontal cortex.	P35-45	THC	Beggiato et al. [123]
Downregulation of drd2 and adora2a gene expression in the adult nucleus accumbens and hippocampus.	P35-57	THC	Cajiao-Manrique et al. [110]
Dorsal hippocampus: decreased GluN2B and GluN2A Ventral hippocampus: Increased GluN2B and mGluR2/3	P35-45	THC	De Felice et al. [105]
Increased AEA, reduced Met-enkephalin and μOR in the nucleus accumbens when tested during adolescence	P28-49	THC	Ellgren et al. [51]
Reduced GABA-Cnr1 expression and increased glutamatergic Cnr1+ cells in the prelimbic prefrontal cortex.	P28-59	THC	Ferland et al. [11]
Decreased expression of GAD67 and CB2R and perineuronal nets in the prefrontal cortex (prelimbic and infralimbic).	P35-49	JWH-018	Izquierdo-Luengo et al. [112]
Increased GABA <sub>B</sub> R2, GAT, pNR2B in the prefrontal cortex; Reduced GAD65 in the prefrontal cortex.	P38-49	WIN	Kirschmann et al. [113]
Downregulation of CB1R expression on vGlut1 terminals in the ventral tegmental area.	P25-58	THC	Kruse et al. [107]
Premature dendritic spine pruning; altered functional gene networks.	P28-49	THC	Miller et al. [116]
Altered gene activation/deactivation in the nucleus accumbens.	P28-44	THC	Orihuel et al. [118]
Decreased GluN1-NMDA levels in the prelimbic prefrontal cortex.	P28-43	THC	Pickel et al. [101]
Increased histone modifications in the amygdala, hippocampus, nucleus accumbens in adolescent-exposed animals.	P35-45, P75-85	THC	Prini et al. [117]
Differential proteomic changes in the hippocampus.	P32-52, P64-84	THC	Quinn et al. [114]
Adolescent exposure: decreased phosphorylation of GSK-3α/β, Akt Thr308, mTOR, p70S6 Kinase, and β-Catenin in the prefrontal cortex. Adult exposure: increased phosphorylation of GSK-3α/β, Akt Ser473, and mTOR in the prefrontal cortex.	P35-45, P65-75	THC	Renard et al. [115]
Altered CB1R G-protein coupling in the amygdala, ventral tegmental area, nucleus accumbens; Altered CREB activity in the hippocampus, prefrontal cortex, and nucleus accumbens.	P35-45	THC	Rubino et al. [121]
Reduced CB1R binding, lower AEA and higher 2-AG; higher levels of GluN2B and GluA1.	P35-45	THC	Rubino et al. [100]
Reduced CB1R, GABA-AR, and glutamate receptor protein level in the prefrontal cortex, dorsal hippocampus, and ventral tegmental area.	P32-51	THC	Stringfield et al. [24]
Increased striatal levels of CB1R protein expression independent of sex. Changes in hippocampal CB1R levels varied by sex.	P35-75	THC	Weed et al. [119]
Reduced GAD67 in CCK- and PV-positive interneurons in the prefrontal cortex; Reduced basal levels of GABA.	P35-45	THC	Zamberletti et al. [111]
Increased pro-inflammatory markers in the prefrontal cortex: TNF-α, iNOS, COX-2; Reduced anti-inflammatory markers in the prefrontal cortex: IL-10.	P35-45	THC	Zamberletti et al. [122]

2-AG 2-arachidonoylglycerol, adora2a adenosine A2A receptor gene, AEA anandamide, Akt Ser473 protein kinase B at serine 473, Akt Thr308 protein kinase B at threonine 308, Arc activity-regulated cytoskeleton-associated protein, β-Catenin catenin beta-1 protein, CB1R cannabinoid type 1 receptor, CB2R cannabinoid type 2 receptor, CCK cholecystokinin, Cnr1 cannabinoid receptor 1 [human], COX-2 cyclooxygenase-2, CREB cyclic AMP-responsive element binding protein, drd2 dopamine receptor D2 gene, GABA gamma-aminobutyric acid, GABA-AR gamma-aminobutyric acid type A receptor, GABABR2 gamma-aminobutyric acid B receptor subunit R2, GAD65 glutamic acid decarboxylase 65, GAD67 glutamic acid decarboxylase 67, GAT gamma-aminobutyric acid transporter, GluA1 glutamate ionotropic receptor AMPA type subunit 1, GluN1 glutamate ionotropic receptor NMDA type subunit 1, GluN2A glutamate receptor ionotropic NMDA 2A, GluN2B glutamate receptor ionotropic NMDA 2B, GSK-3α/β glycogen synthase kinase-3 alpha/beta, IL-10 interleukin 10, iNOS inducible nitric oxide synthase, Met-enkephalin methionine-enkephalin, mGluR2/3 metabotropic glutamate receptor 2/3, mTOR mammalian target of rapamycin, NMDA N-methyl-D-aspartate, P postnatal day, p-CREB phosphorylated cyclic AMP-responsive element binding protein, pNR2B phosphorylated N-methyl-D-aspartate receptor subtype 2B, PV parvalbumin, TNF-α Tumor necrosis factor alpha, vGAT1 vesicular glutamate transporter 1, μOR mu-opioid receptor.

such schizophrenia-spectrum disorders [9, 10, 13, 14, 17] and deficits in cognitive abilities later in life. Both short- and long-term effects on cortical function and its regulation of cognition are expected to emerge following cannabis exposure during adolescence [36, 43]. Unfortunately, studying the long-term impact of frequent cannabinoid use during adolescence presents several challenges, including the extended time frame required to assess long-term effects and difficulties accounting for key factors such as amount of cannabis intake, route of administration, frequency of use, and other environmental influences. Additionally, reliance on self-report data may introduce inaccuracies. Large-scale, long-term studies, such as the Adolescent Brain Cognitive Development (ABCD) Study, help to address these issues by collecting extensive data on over 10,000 children, over ten years. This allows

researchers to track how cannabis use during adolescence impacts behavior and cognition into adulthood. While the study is ongoing, some data has already been examined (Table 3).

Analysis of a subset of 13–14-year-olds in the ABCD study found that those who self-reported cannabis users in the past year, and/or had cannabinoids detected in hair samples, had more impaired episodic memory than demographically matched controls [125]. Higher usage was associated with worse performance on tasks involving verbal, inhibitory, and memory related tasks, similar to findings from other studies [11, 12, 126, 127]. Other studies have shown that cannabis use affects cognitive processes like verbal episodic memory to a similar degree in both adolescents (16–17 years old) and adults (26–29 years old) [128], and these deficits could be reversed after 2–3 weeks of abstinence [129]. Data from

**Table 3.** Impact of chronic and acute cannabis exposure during adolescence in human subjects.

Human Studies	Age	Drug	References
<b>Chronic</b>			
Tested in adulthood and found impairments in reaction time of early users (< 16 y/o).	12–16 y/o vs. >16 y/o	THC	Ehrenreich et al. [126]
Cannabis users exhibited riskier decision making and impulsivity in adulthood compared to non-frequent user age-matched controls.	Average age of initiation: 16.4 y/o	Used cannabis for a minimum of 25 days/month for 5 yrs	Ferland et al. [11]
Regular use (> 1/week) led to poorer performance on attention and spatial working memory in adolescents who were tested.	13–18 y/o	Cannabis	Harvey et al. [12]
Cannabis use resulted in lower episodic memory scores than in healthy controls. More cannabis use was associated with worse performance on verbal, inhibitory, working and episodic memory tasks.	13–14 y/o	Cannabis	Wade et al. [125]
Higher cannabis use was associated with worse decision making and episodic memory one year later.	14–17 y/o	Cannabis	Duperrouzel et al. [127]
Cannabis users in both age groups showed poorer verbal episodic memory. No effects were observed in spatial working memory or response inhibition.	16–17 y/o vs. 26–29 y/o	Cannabis	Lawn et al. [128]
Cannabis users showed poorer verbal learning, working memory, and attention. Deficits in attention accuracy remained apparent after weeks of abstinence.	15–19 y/o	Cannabis	Hanson et al. [129]
<b>Acute</b>			
No differences between adolescents and adults on psychotomimetic effects, verbal memory, or subjective effects. No differences in effect of CBD.	16–17 y/o vs. 26–29 y/o	THC and THC + CBD	Lawn et al. [128]
Both age groups showed THC-induced reductions in network-connectivity in default mode within hippocampal and limbic striatal networks.	16–17 y/o vs. 26–29 y/o	THC and THC + CBD	Ertl et al. [130]
Adolescents showed impaired response inhibition and satiety, adults had more cognitive impairments in memory.	16–17 y/o vs. 24–28 y/o	Cannabis vaporized (0.89 mg/kg)	Mokrysz et al. [133]
Adolescents showed more impairments in reaction time, response accuracy, and time perception. EEG data revealed a reduction in P300 amplitude in a THC dose-dependent manner.	18–20 y/o vs. 30–40 y/o	THC oral (7.5 mg and 15 mg)	Murray et al. [132]

EEG electroencephalography, P300 component of EEG event related potential, P postnatal day.

these studies raises important questions about the specificity and reversibility of these effects, and more studies are needed to explore this further.

To explore differences in cannabinoid responses across developmental stages, researchers can examine the acute effects of  $\Delta^9$ -THC under controlled conditions, at different points during adolescence, as well as in later stages of maturation. This approach allows for control over important factors (e.g., dose, recency of exposure) while assessing differences in sensitivity across age groups. The few studies that have conducted such experiments have shown mixed findings. While some research has shown no differences in neural, cognitive, or subjective effects of  $\Delta^9$ -THC between adolescents (16–17 years old) and adults (26–29 years old) [128, 130], other studies suggest distinct age-related responses [131, 132]. For example, one study found that adolescents experienced greater impairments in response inhibition and satiety, while adults showed more memory-related impairments following acute cannabis administration [133]. Another study demonstrated that adolescents/young adults (18–20 years old) exhibited greater sensitivity to acute  $\Delta^9$ -THC, showing impairments in response inhibition, time perception, and altered neural activity measured by EEG during an attention task, which were not observed in adults (30–40 years old) [132]. These results suggest that certain cognitive and neural processes may be more vulnerable to acute  $\Delta^9$ -THC exposure during adolescence, while others may be less affected by age. Further studies are

needed to better understand the nuances of age-related sensitivity to  $\Delta^9$ -THC.

A major detrimental impact resulting from chronic cannabis use is the development of cognitive deficits within the working memory and decision-making domains [134–137]. Data from rodent models of chronic cannabinoid exposure (see Section 3.3) indicate that sustained CB1 receptor stimulation could account for the onset of cognitive deficits observed [19]. While the level of CB1 receptor availability was not correlated with the duration or the age of onset of cannabis use [138], current available data shows that the degree of cognitive deficits observed in chronic cannabis users is linked with the extent of CB1 receptor stimulation in a dose-dependent manner [138, 139]. Accordingly, the density of CB1 receptors begins to recover within days of abstinence [140] reaching control levels after one month of abstinence [139], which coincides with the recovery of cognitive function [141, 142]. Similarly, the impact of chronic cannabis use during adolescence have been well studied over the years, with increasing research pointing toward negative impacts on pre-frontal cortical-dependent cognitive processes (see [22]). For example, cannabis users who begin prior to age 16 develop attentional deficits that are not apparent in late onset users [126]. This observation is consistent with data obtained from regular cannabis users aged 13–18 exhibiting poorer performance in cognitive tasks within the attention and spatial working memory domains [12]. Long-lasting cognitive dysregulation observed in

regular cannabis users within the adolescent population include attention deficits and impairments in executive function [135, 143]. However, future studies are needed to establish a causal link by assessing the extent to which genetic factors and childhood environments contribute to the lasting negative impact of regular cannabis use within the adolescent population (see [22]). As discussed above, there are several additional variables that need to be accounted for such as the amount, route, and frequency of cannabis intake.

## PRACTICAL CONSIDERATIONS AND CONCLUDING REMARKS

Extensive studies in both humans and rodent models have been conducted over the years to reveal the impact of repeated cannabis exposure during sensitive periods of brain development and maturation. Collectively, the data all point towards a detrimental effect on a series of cognitive processes that are reliant on the prefrontal cortex and its functional connectivity within the corticolimbic network [16, 19, 26, 131]. As mentioned in Section 1, many reviews have been written in the past two decades highlighting the long list of behavioral changes resulting from repeated cannabis and cannabinoid exposure during different stages of brain development [19–30]. For instance, adolescents are typically more sensitive to the effects of  $\Delta^9$ -THC and cannabinoids than adults both in rodents [45, 114, 144–149] and humans [132, 133, 150], which coincide with the higher level of CB1R expression in the brain of adolescents relative to adults (Fig. 1). Certainly, a developmental framework is needed to enable the distinction of age-dependent vs. age-independent effects of  $\Delta^9$ -THC and to uncover the underlying mechanisms driving the end of a sensitive period. However, it is also crucial to incorporate mechanistic aspects of the brain endocannabinoid system and how disruption of tonic versus phasic endocannabinoid signaling by  $\Delta^9$ -THC exposure contributes to alter synaptic plasticity [151–156]. Data from a recent study further suggest that the impact of  $\Delta^9$ -THC on CB1R function could be linked to the proximity to the effectors regardless of its expression level [157]. Using an in vivo pharmacological treatment paradigm that induces behavioral tolerance, it was found that the dose-dependent reduction of CB1R content in axonal boutons observed following THC exposure in adolescent mice has little functional consequences on phasic endocannabinoid synaptic transmission [157]. Instead, adolescent THC exposure decreased the intra/perisynaptic CB1R population and the nanoscale receptor-to-effector ratio, which disrupts the nanoscale functional organization required for sustaining normal synaptic cannabinoid tone [157]. In this regard, establishing how nanodomain-specific processes are mechanistically linked to phasic vs. tonic control of synaptic function [157] and its impact on synaptic plasticity could provide clues on how  $\Delta^9$ -THC exposure affects neural circuit function during development [158–161]. Together, such knowledge will provide unique insights on why a developmental window is particularly vulnerable to environmental influences like cannabis and  $\Delta^9$ -THC, and whether the complex landscape of genes-environment interaction contributes to the underpinnings of individual differences. A mechanistic developmental analysis of cannabis/cannabinoid-sensitive neural circuits will delineate a much-needed research paradigm to uncover the distinct neurobiological effects of  $\Delta^9$ -THC through the lifespan.

## REFERENCES

1. Gaoni YMR. Isolation, structure, and partial synthesis of an active constituent of hashish. *J Am Chem Soc.* 1964;86:1646.
2. ElSohly MA, Gul W. Chapter 1: constituents of *Cannabis sativa*, in, R Pertwee, Editor. *Handbook of Cannabis*. Oxford University Press; 2014. pp. 3–22.
3. Rock EM, Parker LA. Constituents of *Cannabis sativa*. *Adv Exp Med Biol.* 2021;1264:1–13.
4. Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci Biobehav Rev.* 2003;27:3–18.
5. Casey BJ, Giedd JN, Thomas KM. Structural and functional brain development and its relation to cognitive development. *Biol Psychol.* 2000;54:241–57.
6. Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *Am J Psychiatry.* 2003;160:1041–52.
7. Spear LP. The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev.* 2000;24:417–63.
8. Crews F, He J, Hodge C. Adolescent cortical development: a critical period of vulnerability for addiction. *Pharmacol Biochem Behav.* 2007;86:189–99.
9. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. *Cannabis* use in adolescence and risk for adult psychosis: longitudinal prospective study. *Br J Psychiatry.* 2002;325:1212–3.
10. Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, et al. Moderation of the effect of adolescent-onset *Cannabis* use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol Psychiatry.* 2005;57:1117–27.
11. Ferland JN, Ellis RJ, Betts G, Silveira MM, de Firmino JB, Winstanley CA, et al. Long-Term Outcomes of adolescent THC exposure on translational cognitive measures in adulthood in an animal model and computational assessment of human data. *JAMA Psychiatry.* 2023;80:66–76.
12. Harvey MA, Sellman JD, Porter RJ, Frampton CM. The relationship between non-acute adolescent *Cannabis* use and cognition. *Drug Alcohol Rev.* 2007;26:309–19.
13. Sewell RA, Ranganathan M, D'Souza DC. Cannabinoids and psychosis. *Int Rev Psychiatry.* 2009;21:152–62.
14. Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported *Cannabis* use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *Br J Psychiatry.* 2002;325:1199.
15. Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, et al. The contribution of *Cannabis* use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry.* 2019;6:427–36.
16. Murray RM, Englund A, Abi-Dargham A, Lewis DA, Di Forti M, Davies C, et al. *Cannabis*-associated psychosis: neural substrate and clinical impact. *Neuropharmacology.* 2017;124:89–104.
17. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. *Cannabis* use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet.* 2007;370:319–28.
18. Murray RM, Di Forti M. *Cannabis* and psychosis: what degree of proof do we require? *Biol Psychiatry.* 2016;79:514–5.
19. Caballero A, Tseng KY. Association of *Cannabis* use during adolescence, pre-frontal CB1 receptor signaling, and schizophrenia. *Front Pharmacol.* 2012;3:101.
20. Hurd YL, Manzoni OJ, Pletnikov MV, Lee FS, Bhattacharyya S, Melis M. *Cannabis* and the developing brain: insights into its long-lasting effects. *J Neurosci.* 2019;39:8250–8.
21. Scheyen AF, Melis M, Trezza V, Manzoni OJJ. Consequences of perinatal *Cannabis* exposure. *Trends Neurosci.* 2019;42:871–84.
22. Molla HM, Tseng KY. Neural substrates underlying the negative impact of cannabinoid exposure during adolescence. *Pharmacol Biochem Behav.* 2020;195:172965.
23. Bara A, Ferland JN, Rompala G, Szutorisz H, Hurd YL. *Cannabis* and synaptic reprogramming of the developing brain. *Nat Rev Neurosci.* 2021;22:423–38.
24. Stringfield SJ, Torregrossa MM. Intravenous self-administration of delta-9-THC in adolescent rats produces long-lasting alterations in behavior and receptor protein expression. *Psychopharmacology.* 2021;238:305–19.
25. Peters KZ, Zlebnik NE, Cheer JF. *Cannabis* exposure during adolescence: a uniquely sensitive period for neurobiological effects. *Int Rev Neurobiol.* 2022;161:95–120.
26. Li Z, Mukherjee D, Duric B, Austin-Zimmerman I, Trotta G, Spinazzola E, et al. Systematic review and meta-analysis on the effects of chronic peri-adolescent cannabinoid exposure on schizophrenia-like behaviour in rodents. *Mol Psychiatry.* 2024;30:285–95.
27. Rubino T, Parolaro D. The impact of exposure to cannabinoids in adolescence: insights from animal models. *Biol Psychiatry.* 2016;79:578–85.
28. Bossong MG, Niesink RJ. Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of *Cannabis*-induced schizophrenia. *Prog Neurobiol.* 2010;92:370–85.
29. Ferland JN, Hurd YL. Deconstructing the neurobiology of *Cannabis* use disorder. *Nat Neurosci.* 2020;23:600–10.
30. Renard J, Rushlow WJ, Laviolette SR. Effects of adolescent THC exposure on the prefrontal GABAergic system: implications for schizophrenia-related psychopathology. *Front Psychiatry.* 2018;9:281.

31. Caballero A, Tseng KY. GABAergic function as a limiting factor for prefrontal maturation during adolescence. *Trends Neurosci.* 2016;39:441–8.
32. Colizzi M, McGuire P, Pertwee RG, Bhattacharya S. Effect of *Cannabis* on glutamate signalling in the brain: a systematic review of human and animal evidence. *Neurosci Biobehav Rev.* 2016;64:359–81.
33. Devane WA, Dysarz FA 3rd, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol.* 1988;34:605–13.
34. Mallet PE, Beninger RJ. The cannabinoid CB1 receptor antagonist SR141716A attenuates the memory impairment produced by delta9-tetrahydrocannabinol or anandamide. *Psychopharmacology.* 1998;140:11–19.
35. Raver SM, Keller A. Permanent suppression of cortical oscillations in mice after adolescent exposure to cannabinoids: receptor mechanisms. *Neuropharmacology.* 2014;86:161–73.
36. D’Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology.* 2004;29:1558–72.
37. Englund A, Atakan Z, Kralj A, Tunstall N, Murray R, Morrison P. The effect of five day dosing with THCV on THC-induced cognitive, psychological and physiological effects in healthy male human volunteers: a placebo-controlled, double-blind, crossover pilot trial. *J Psychopharmacol.* 2016;30:140–51.
38. Horder J, Browning M, Di Simplicio M, Cowen PJ, Harmer CJ. Effects of 7 days of treatment with the cannabinoid type 1 receptor antagonist, rimonabant, on emotional processing. *J Psychopharmacol.* 2012;26:125–32.
39. Zuurman L, Roy C, Schoemaker RC, Amatsaleh A, Guimaeres L, Pinquier JL, et al. Inhibition of THC-induced effects on the central nervous system and heart rate by a novel CB1 receptor antagonist AVE1625. *J Psychopharmacol.* 2010;24:363–71.
40. Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. *J Neurosci.* 1991;11:563–83.
41. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, et al. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci USA.* 1990;87:1932–6.
42. Lovering DM. Presynaptic modulation by endocannabinoids. *Handb Exp Pharmacol.* 2008;184:435–77.
43. Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. *Physiol Rev.* 2003;83:1017–66.
44. Regehr WG, Carey MR, Best AR. Activity-dependent regulation of synapses by retrograde messengers. *Neuron.* 2009;63:154–70.
45. Cass DK, Flores-Barrera E, Thomases DR, Vital WF, Caballero A, Tseng KY. CB1 cannabinoid receptor stimulation during adolescence impairs the maturation of GABA function in the adult rat prefrontal cortex. *Mol Psychiatry.* 2014;19:536–43.
46. Molla HM, Miguelez Fernandez AMM, Tseng KY. Late-adolescent onset of prefrontal endocannabinoid control of hippocampal and amygdalar inputs and its impact on trace-fear conditioning behavior. *Neuropsychopharmacology.* 2024;49:1417–24.
47. Choi K, Le T, McGuire J, Xing G, Zhang L, Li H, et al. Expression pattern of the cannabinoid receptor genes in the frontal cortex of mood disorder patients and mice selectively bred for high and low fear. *J Psychiatr Res.* 2012;46:882–9.
48. Long LE, Lind J, Webster M, Weickert CS. Developmental trajectory of the endocannabinoid system in human dorsolateral prefrontal cortex. *BMC Neurosci.* 2012;13:87.
49. Heng L, Beverley JA, Steiner H, Tseng KY. Differential developmental trajectories for CB1 cannabinoid receptor expression in limbic/associative and sensorimotor cortical areas. *Synapse.* 2011;65:278–86.
50. Chesworth R, Long LE, Weickert CS, Karl T. The endocannabinoid system across postnatal development in transmembrane domain neuregulin 1 mutant mice. *Front Psychiatry.* 2018;9:11.
51. Ellgren M, Artmann A, Tkalych O, Gupta A, Hansen HS, Hansen SH, et al. Dynamic changes of the endogenous cannabinoid and opioid mesocorticolimbic systems during adolescence: THC effects. *Eur Neuropsychopharmacol.* 2008;18:826–34.
52. Yang S, Tseng KY. Maturation of corticolimbic functional connectivity during sensitive periods of brain development. *Curr Top Behav Neurosci.* 2022;53:37–53.
53. Castillo PE, Younts TJ, Chavez AE, Hashimoto-dani Y. Endocannabinoid signaling and synaptic function. *Neuron.* 2012;76:70–81.
54. Kano M, Hashimoto K, Tabata T. Type-1 metabotropic glutamate receptor in cerebellar Purkinje cells: a key molecule responsible for long-term depression, endocannabinoid signalling and synapse elimination. *Philos Trans R Soc Lond B Biol Sci.* 2008;363:2173–86.
55. Van Waes V, Beverley JA, Siman H, Tseng KY, Steiner H. CB1 cannabinoid receptor expression in the striatum: association with corticostratial circuits and developmental regulation. *Front Pharmacol.* 2012;3:21.
56. Andersen SL. Sensitive periods of brain development and preventive interventions. 2021/08/14 ed. *Current Topics in Behavioral Neurosciences.* Vol. 53. 2022.
57. Berghuis P, Dobcsay MB, Wang X, Spano S, Ledda F, Sousa KM, et al. Endocannabinoids regulate interneuron migration and morphogenesis by transactivating the TrkB receptor. *Proc Natl Acad Sci USA.* 2005;102:19115–20.
58. Berghuis P, Rajnicek AM, Morozov YM, Ross RA, Mulder J, Urban GM, et al. Hardwiring the brain: endocannabinoids shape neuronal connectivity. *Science.* 2007;316:1212–6.
59. Mulder J, Aguado T, Keimpema E, Barabas K, Ballester Rosado CJ, Nguyen L, et al. Endocannabinoid signaling controls pyramidal cell specification and long-range axon patterning. *Proc Natl Acad Sci USA.* 2008;105:8760–5.
60. Watson S, Chambers D, Hobbs C, Doherty P, Graham A. The endocannabinoid receptor, CB1, is required for normal axonal growth and fasciculation. *Mol Cell Neurosci.* 2008;38:89–97.
61. Frau R, Miczan V, Traccis F, Aroni S, Pongor Cl, Saba P, et al. Prenatal THC exposure produces a hyperdopaminergic phenotype rescued by pregnenolone. *Nat Neurosci.* 2019;22:1975–85.
62. Rodriguez de Fonseca F, Hernandez ML, de Miguel R, Fernandez-Ruiz JJ, Ramos JA. Early changes in the development of dopaminergic neurotransmission after maternal exposure to cannabinoids. *Pharmacol Biochem Behav.* 1992;41:469–74.
63. Scheyer AF, Borsig M, Wager-Miller J, Pelissier-Alicot AL, Murphy MN, Mackie K, et al. Cannabinoid exposure via lactation in rats disrupts perinatal programming of the gamma-aminobutyric acid trajectory and select early-life behaviors. *Biol Psychiatry.* 2020;87:666–77.
64. de Salas-Quiroga A, Diaz-Alonso J, Garcia-Rincon D, Remmers F, Vega D, Gomez-Canales M, et al. Prenatal exposure to cannabinoids evokes long-lasting functional alterations by targeting CB1 receptors on developing cortical neurons. *Proc Natl Acad Sci USA.* 2015;112:13693–8.
65. de Salas-Quiroga A, Garcia-Rincon D, Gomez-Dominguez D, Valero M, Simon-Sanchez S, Paraiso-Luna J, et al. Long-term hippocampal interneuronopathy drives sex-dimorphic spatial memory impairment induced by prenatal THC exposure. *Neuropsychopharmacology.* 2020;45:877–86.
66. Spano MS, Ellgren M, Wang X, Hurd YL. Prenatal *Cannabis* exposure increases heroin seeking with allostatic changes in limbic enkephalin systems in adulthood. *Biol Psychiatry.* 2007;61:554–63.
67. Tortoriello G, Morris CV, Alpar A, Fuzik J, Shirran SL, Calvignoni D, et al. Miswiring the brain: Delta9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway. *EMBO J.* 2014;33:668–85.
68. Ryan KS, Karpf JA, Chan CN, Hagen OL, McFarland TJ, Urian JW, et al. Prenatal delta-9-tetrahydrocannabinol exposure alters fetal neurodevelopment in rhesus macaques. *Sci Rep.* 2024;14:5808.
69. Chen CY, O’Brien MS, Anthony JC. Who becomes *Cannabis* dependent soon after onset of use? Epidemiological evidence from the United States: 2000–2001. *Drug Alcohol Depend.* 2005;79:11–22.
70. Martin GL. Marijuana: the effects on pregnancy, the fetus, and the newborn. *J Perinatol.* 2020;40:1470–6.
71. Baranger DAA. Evaluating evidence supporting an effect of prenatal *Cannabis* exposure on white matter integrity. *Biol Psychiatry Glob Open Sci.* 2024;4:101–2.
72. Best JR, Miller PH. A developmental perspective on executive function. *Child Dev.* 2010;81:1641–60.
73. Tseng KY, Chambers RA, Lipska BK. The neonatal ventral hippocampal lesion as a heuristic neurodevelopmental model of schizophrenia. *Behav Brain Res.* 2009;204:295–305.
74. Scheyer AF, Borsig M, Pelissier-Alicot AL, Manzoni OJJ. Maternal exposure to the cannabinoid agonist WIN 55,12,2 during lactation induces lasting behavioral and synaptic alterations in the rat adult offspring of both sexes. *eNeuro.* 2020;7:ENEURO.0144-20.2020.
75. Scheyer AF, Borsig M, Pelissier-Alicot AL, Manzoni OJJ. Perinatal THC exposure via lactation induces lasting alterations to social behavior and prefrontal cortex function in rats at adulthood. *Neuropsychopharmacology.* 2020;45:1826–33.
76. Lujan MA, Young-Morrison R, Aroni S, Katona I, Melis M, Cheer JF. Dynamic overrepresentation of accumbal cues in food- and opioid-seeking rats after prenatal THC exposure. *Sci Adv.* 2024;10:eadq5652.
77. Peterson CS, Baglot SL, Sallam NA, Mina S, Hill MN, Borgland SL. Oral pre- and early postnatal *Cannabis* exposure disinhibits ventral tegmental area dopamine neuron activity but does not influence cocaine preference in offspring in mice. *J Neurosci Res.* 2024;102:e25369.
78. Frau R, Melis M. Sex-specific susceptibility to psychotic-like states provoked by prenatal THC exposure: reversal by pregnenolone. *J Neuroendocrinol.* 2023;35:e13240.
79. DiNieri JA, Wang X, Szutorisz H, Spano SM, Kaur J, Casaccia P, et al. Maternal *Cannabis* use alters ventral striatal dopamine D2 gene regulation in the offspring. *Biol Psychiatry.* 2011;70:763–9.

80. Lew SE, Tseng KY. Dopamine modulation of GABAergic function enables network stability and input selectivity for sustaining working memory in a computational model of the prefrontal cortex. *Neuropharmacology*. 2014;39:3067–76.
81. Flores-Barrera E, Thomases DR, Heng LJ, Cass DK, Caballero A, Tseng KY. Late adolescent expression of GluN2B transmission in the prefrontal cortex is input-specific and requires postsynaptic protein kinase A and D1 dopamine receptor signaling. *Biol Psychiatry*. 2014;75:508–16.
82. Satterthwaite TD, Wolf DH, Erus G, Ruparel K, Elliott MA, Gennatas ED, et al. Functional maturation of the executive system during adolescence. *J Neurosci*. 2013;33:16249–61.
83. Gee DG, Humphreys KL, Flannery J, Goff B, Telzer EH, Shapiro M, et al. A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. *J Neurosci*. 2013;33:4584–93.
84. Swartz JR, Phan KL, Angstadt M, Klumpp H, Fitzgerald KD, Monk CS. Altered activation of the rostral anterior cingulate cortex in the context of emotional face distractors in children and adolescents with anxiety disorders. *Depress Anxiety*. 2014;31:870–9.
85. Paus T, Zijdenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, et al. Structural maturation of neural pathways in children and adolescents: in vivo study. *Science*. 1999;283:1908–11.
86. Sowell ER, Thompson PM, Holmes CJ, Batt R, Jernigan TL, Toga AW. Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *NeuroImage*. 1999;9:587–97.
87. Floresco SB, Seamans JK, Phillips AG. Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. *J Neurosci*. 1997;17:1880–90.
88. Ishikawa A, Nakamura S. Convergence and interaction of hippocampal and amygdalar projections within the prefrontal cortex in the rat. *J Neurosci*. 2003;23:9987–95.
89. Tse MT, Piantadosi PT, Floresco SB. Prefrontal cortical gamma-aminobutyric acid transmission and cognitive function: drawing links to schizophrenia from pre-clinical research. *Biol Psychiatry*. 2015;77:929–39.
90. Calabro FJ, Murty VP, Jalbrzikowski M, Tervo-Clemmens B, Luna B. Development of hippocampal-prefrontal cortex interactions through adolescence. *Cereb Cortex*. 2020;30:1548–58.
91. Murty VP, Calabro F, Luna B. The role of experience in adolescent cognitive development: integration of executive, memory, and mesolimbic systems. *Neurosci Biobehav Rev*. 2016;70:46–58.
92. Larsen B, Cui Z, Adebimpe A, Pines A, Alexander-Bloch A, Bertolero M, et al. A developmental reduction of the excitation:inhibition ratio in association cortex during adolescence. *Sci Adv*. 2022;8:eabj8750.
93. Caballero A, Orozco A, Tseng KY. Developmental regulation of excitatory-inhibitory synaptic balance in the prefrontal cortex during adolescence. *Semin Cell Dev Biol*. 2021;118:60–63.
94. Caballero A, Flores-Barrera E, Thomases DR, Tseng KY. Downregulation of parvalbumin expression in the prefrontal cortex during adolescence causes enduring prefrontal disinhibition in adulthood. *Neuropharmacology*. 2020;45:1527–35.
95. Cass DK, Thomases DR, Caballero A, Tseng KY. Developmental disruption of gamma-aminobutyric acid function in the medial prefrontal cortex by noncontingent cocaine exposure during early adolescence. *Biol Psychiatry*. 2013;74:490–501.
96. Flores-Barrera E, Thomases DR, Tseng KY. MK-801 exposure during adolescence elicits enduring disruption of prefrontal E-I balance and its control of fear extinction behavior. *J Neurosci*. 2020;40:4881–7.
97. Thomases DR, Cass DK, Meyer JD, Caballero A, Tseng KY. Early adolescent MK-801 exposure impairs the maturation of ventral hippocampal control of basolateral amygdala drive in the adult prefrontal cortex. *J Neurosci*. 2014;34:9059–66.
98. Thomases DR, Cass DK, Tseng KY. Periadolescent exposure to the NMDA receptor antagonist MK-801 impairs the functional maturation of local GABAergic circuits in the adult prefrontal cortex. *J Neurosci*. 2013;33:26–34.
99. Cuccuruzzo B, Zamberletti E, Nazzaro C, Prini P, Trusel M, Grilli M, et al. Adult cellular neuroadaptations induced by adolescent THC exposure in female rats are rescued by enhancing anandamide signaling. *Int J Neuropsychopharmacol*. 2018;21:1014–24.
100. Rubino T, Prini P, Piscitelli F, Zamberletti E, Trusel M, Melis M, et al. Adolescent exposure to THC in female rats disrupts developmental changes in the prefrontal cortex. *Neurobiol Dis*. 2015;73:60–69.
101. Pickel VM, Bourie F, Chan J, Mackie K, Lane DA, Wang G. Chronic adolescent exposure to Δ<sup>9</sup>-tetrahydrocannabinol decreases NMDA current and extra-synaptic plasmalemmal density of NMDA GluN1 subunits in the prelimbic cortex of adult male mice. *Neuropharmacology*. 2020;45:374–83.
102. Miguelez Fernandez AMM, Molla HM, Thomases DR, Tseng KY. Prefrontal alpha<sub>7</sub>AChR signaling differentially modulates afferent drive and trace fear conditioning behavior in adolescent and adult rats. *J Neurosci*. 2021;41:1908–16.
103. Heng LJ, Markham JA, Hu XT, Tseng KY. Concurrent upregulation of post-synaptic L-type Ca(2+) channel function and protein kinase A signaling is required for the peradolescent facilitation of Ca(2+) plateau potentials and dopamine D1 receptor modulation in the prefrontal cortex. *Neuropharmacology*. 2011;60:953–62.
104. Tseng KY, O'Donnell P. Post-pubertal emergence of prefrontal cortical up states induced by D1-NMDA co-activation. *Cereb Cortex*. 2005;15:49–57.
105. De Felice M, Chen C, Rodriguez-Ruiz M, Szkludlarek HJ, Lam M, Sert S, et al. Adolescent delta-9-tetrahydrocannabinol exposure induces differential acute and long-term neuronal and molecular disturbances in dorsal vs. ventral hippocampal subregions. *Neuropharmacology*. 2023;48:540–51.
106. De Gregorio D, Dean Conway J, Canul ML, Posa L, Bambico FR, Gobbi G. Effects of chronic exposure to low doses of delta-9-tetrahydrocannabinol in adolescence and adulthood on serotonin/norepinephrine neurotransmission and emotional behaviors. *Int J Neuropsychopharmacol*. 2020;23:751–61.
107. Kruse LC, Cao JK, Viray K, Stella N, Clark JJ. Voluntary oral consumption of delta(9)-tetrahydrocannabinol by adolescent rats impairs reward-predictive cue behaviors in adulthood. *Neuropharmacology*. 2019;44:1406–14.
108. Pistis M, Perra S, Pillolla G, Melis M, Muntoni AL, Gessa GL. Adolescent exposure to cannabinoids induces long-lasting changes in the response to drugs of abuse of rat midbrain dopamine neurons. *Biol Psychiatry*. 2004;56:86–94.
109. Scherma M, Dessi C, Muntoni AL, Lecca S, Satta V, Luchicchi A, et al. Adolescent delta(9)-tetrahydrocannabinol exposure alters WIN55,212-2 self-administration in adult rats. *Neuropharmacology*. 2016;41:1416–26.
110. Cajiao-Manrique MDM, Casado-Anguera V, Garcia-Blanco A, Maldonado R, Martin-Garcia E. THC exposure during adolescence increases impulsivity-like behavior in adulthood in a WIN 55,212-2 self-administration mouse model. *Front Psychiatry*. 2023;14:1148993.
111. Zamberletti E, Beggiato S, Steardo L Jr, Prini P, Antonelli T, Ferraro L, et al. Alterations of prefrontal cortex GABAergic transmission in the complex psychotic-like phenotype induced by adolescent delta-9-tetrahydrocannabinol exposure in rats. *Neurobiol Dis*. 2014;63:35–47.
112. Izquierdo-Luengo C, Ten-Blanco M, Ponce-Renilla M, Perezan R, Perea-Perez I, Berrendero F. Adolescent exposure to the Spice/K2 cannabinoid JWH-018 impairs sensorimotor gating and alters cortical perineuronal nets in a sex-dependent manner. *Transl Psychiatry*. 2023;13:176.
113. Kirschmann EK, Pollock MW, Nagarajan V, Torregrossa MM. Effects of adolescent cannabinoid self-administration in rats on addiction-related behaviors and working memory. *Neuropharmacology*. 2017;42:989–1000.
114. Quinn HR, Matsumoto I, Callaghan PD, Long LE, Arnold JC, Gunasekaran N, et al. Adolescent rats find repeated delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. *Neuropharmacology*. 2008;33:1113–26.
115. Renard J, Rosen LG, Loureiro M, De Oliveira C, Schmid S, Rushlow WJ, et al. Adolescent cannabinoid exposure induces a persistent sub-cortical hyperdopaminergic state and associated molecular adaptations in the prefrontal cortex. *Cereb Cortex*. 2017;27:1297–310.
116. Miller ML, Chadwick B, Dickstein DL, Purushothaman I, Egervari G, Rahman T, et al. Adolescent exposure to delta(9)-tetrahydrocannabinol alters the transcriptional trajectory and dendritic architecture of prefrontal pyramidal neurons. *Mol Psychiatry*. 2019;24:588–600.
117. Prini P, Penna F, Sciuicciati E, Alberio T, Rubino T. Chronic delta(8)-THC exposure differently affects histone modifications in the adolescent and adult rat brain. *Int J Mol Sci*. 2017;18:2094.
118. Orihuel J, Capellan R, Roura-Martinez D, Ucha M, Ambrosio E, Higuera-Matas A. Delta-9-tetrahydrocannabinol during adolescence reprograms the nucleus accumbens transcriptome, affecting reward processing, impulsivity, and specific aspects of cocaine addiction-like behavior in a sex-dependent manner. *Int J Neuropsychopharmacol*. 2021;24:920–33.
119. Weed PF, Filipeanu CM, Ketchum MJ, Winsauer PJ. Chronic delta-9-tetrahydrocannabinol during adolescence differentially modulates striatal CB1 receptor expression and the acute and chronic effects on learning in adult rats. *J Pharmacol Exp Ther*. 2016;356:20–31.
120. Ballinger MD, Saito A, Abazyan B, Taniguchi Y, Huang CH, Ito K, et al. Adolescent Cannabis exposure interacts with mutant DISC1 to produce impaired adult emotional memory. *Neurobiol Dis*. 2015;82:176–84.
121. Rubino T, Vigano D, Realini N, Guidali C, Braida D, Capurro V, et al. Chronic delta-9-tetrahydrocannabinol during adolescence provokes sex-dependent changes in the emotional profile in adult rats: behavioral and biochemical correlates. *Neuropharmacology*. 2008;33:2760–71.
122. Zamberletti E, Gabaglio M, Prini P, Rubino T, Parolari D. Cortical neuroinflammation contributes to long-term cognitive dysfunctions following adolescent delta-9-tetrahydrocannabinol treatment in female rats. *Eur Neuropsychopharmacol*. 2015;25:2404–15.

123. Beggiato S, Ieraci A, Zuccarini M, Di Iorio P, Schwarcz R, Ferraro L. Alterations in rat prefrontal cortex kynurenic acid levels are involved in the enduring cognitive dysfunctions induced by tetrahydrocannabinol exposure during the adolescence. *Front Psychiatry*. 2022;13:996406.
124. Patrick ME, Fleming CB, Fairlie AM, Lee CM. Cross-fading motives for simultaneous alcohol and marijuana use: associations with young adults' use and consequences across days. *Drug Alcohol Depend*. 2020;213:108077.
125. Wade NE, Wallace AL, Huestis MA, Lisdahl KM, Sullivan RM, Tapert SF. *Cannabis* use and neurocognitive performance at 13–14 years-old: optimizing assessment with hair toxicology in the adolescent brain cognitive development (ABCD) study. *Addict Behav*. 2024;150:107930.
126. Ehrenreich H, Rinn T, Kunert HJ, Moeller MR, Poser W, Schilling L, et al. Specific attentional dysfunction in adults following early start of *Cannabis* use. *Psychopharmacology*. 1999;142:295–301.
127. Duperrouzel JC, Hawes SW, Lopez-Quintero C, Pacheco-Colon I, Coxe S, Hayes T, et al. Adolescent *Cannabis* use and its associations with decision-making and episodic memory: preliminary results from a longitudinal study. *Neuropsychology*. 2019;33:701–10.
128. Lawn W, Trinci K, Mokrysz C, Borissova A, Ofori S, Petrilli K, et al. The acute effects of *Cannabis* with and without cannabidiol in adults and adolescents: a randomised, double-blind, placebo-controlled, crossover experiment. *Addiction*. 2023;118:1282–94.
129. Hanson KL, Winward JL, Schweinsburg AD, Medina KL, Brown SA, Tapert SF. Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence. *Addict Behav*. 2010;35:970–6.
130. Ertl N, Freeman TP, Mokrysz C, Ofori S, Borissova A, Petrilli K, et al. Acute effects of different types of *Cannabis* on young adult and adolescent resting-state brain networks. *Neuropsychopharmacology*. 2024;49:1640–51.
131. Mizrahi R, Watts JJ, Tseng KY. Mechanisms contributing to cognitive deficits in *Cannabis* users. *Neuropharmacology*. 2017;124:84–8.
132. Murray CH, Huang Z, Lee R, de Wit H. Adolescents are more sensitive than adults to acute behavioral and cognitive effects of THC. *Neuropsychopharmacology*. 2022;47:1331–8.
133. Mokrysz C, Freeman TP, Korkki S, Griffiths K, Curran HV. Are adolescents more vulnerable to the harmful effects of *Cannabis* than adults? a placebo-controlled study in human males. *Transl Psychiatry*. 2016;6:e961.
134. Kanayama G, Rogowska J, Pope HG, Gruber SA, Yurgelun-Todd DA. Spatial working memory in heavy *Cannabis* users: a functional magnetic resonance imaging study. *Psychopharmacology*. 2004;176:239–47.
135. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, et al. Persistent *Cannabis* users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci USA*. 2012;109:E2657–64.
136. Schweinsburg AD, Schweinsburg BC, Medina KL, McQueeny T, Brown SA, Tapert SF. The influence of recency of use on fMRI response during spatial working memory in adolescent marijuana users. *J Psychoact Drugs*. 2010;42:401–12.
137. Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, et al. Cognitive functioning of long-term heavy *Cannabis* users seeking treatment. *Jama*. 2002;287:1123–31.
138. Ceccarini J, Kuepper R, Kemels D, van Os J, Henquet C, Van Laere K. [18F]MK-9470 PET measurement of cannabinoid CB1 receptor availability in chronic *Cannabis* users. *Addict Biol*. 2015;20:357–67.
139. Hirvonen J, Goodwin RS, Li CT, Terry GE, Zoghbi SS, Morse C, et al. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily *Cannabis* smokers. *Mol Psychiatry*. 2012;17:642–9.
140. D'Souza DC, Cortes-Briones JA, Ranganathan M, Thurnauer H, Creatura G, Surti T, et al. Rapid changes in CB1 receptor availability in *Cannabis* dependent males after abstinence from *Cannabis*. *Biol Psychiatry Cogn Neuroimaging*. 2016;1:60–7.
141. Pope HG Jr., Gruber AJ, Hudson JL, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term *Cannabis* users. *Arch Gen Psychiatry*. 2001;58:909–15.
142. Schreiner AM, Dunn ME. Residual effects of *Cannabis* use on neurocognitive performance after prolonged abstinence: a meta-analysis. *Exp Clin Psychopharmacol*. 2012;20:420–9.
143. Fontes MA, Bolla KI, Cunha PJ, Almeida PP, Jungerman F, Laranjeira RR, et al. *Cannabis* use before age 15 and subsequent executive functioning. *Br J Psychiatry*. 2011;198:442–7.
144. O'Shea M, Singh ME, McGregor IS, Mallet PE. Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats. *J Psychopharmacol*. 2004;18:502–8.
145. Schneider M, Koch M. Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. *Neuropsychopharmacology*. 2003;28:1760–9.
146. Wiley JL, Evans RL, Grainger DB, Nicholson KL. Age-dependent differences in sensitivity and sensitization to cannabinoids and 'club drugs' in male adolescent and adult rats. *Addict Biol*. 2008;13:277–86.
147. Wiley JL, M O'Connell M, Tokarz ME, Wright MJ Jr. Pharmacological effects of acute and repeated administration of delta(9)-tetrahydrocannabinol in adolescent and adult rats. *J Pharmacol Exp Ther*. 2007;320:1097–105.
148. Gomes FV, Issy AC, Ferreira FR, Viveros MP, Del Bel EA, Guimaraes FS. Cannabidiol attenuates sensorimotor gating disruption and molecular changes induced by chronic antagonism of NMDA receptors in mice. *Int J Neuropsychopharmacol*. 2014;18:pyu041.
149. Jacobs-Brichford E, Manson KF, Roitman JD. Effects of chronic cannabinoid exposure during adolescence on reward preference and mPFC activation in adulthood. *Physiol Behav*. 2019;199:395–404.
150. Cha YM, White AM, Kuhn CM, Wilson WA, Swartzwelder HS. Differential effects of delta9-THC on learning in adolescent and adult rats. *Pharmacol Biochem Behav*. 2006;83:448–55.
151. Hashimoto-dani Y, Ohno-Shosaku T, Kano M. Presynaptic monoacylglycerol lipase activity determines basal endocannabinoid tone and terminates retrograde endocannabinoid signaling in the hippocampus. *J Neurosci*. 2007;27:1211–9.
152. Kim J, Alger BE. Reduction in endocannabinoid tone is a homeostatic mechanism for specific inhibitory synapses. *Nat Neurosci*. 2010;13:592–600.
153. Marcus DJ, Bedse G, Gaulden AD, Ryan JD, Kondev V, Winters ND, et al. Endocannabinoid signaling collapse mediates stress-induced amygdalo-cortical strengthening. *Neuron*. 2020;105:1062–76.e1066.
154. Neu A, Foldy C, Soltesz I. Postsynaptic origin of CB1-dependent tonic inhibition of GABA release at cholecystokinin-positive basket cell to pyramidal cell synapses in the CA1 region of the rat hippocampus. *J Physiol*. 2007;578:233–47.
155. Petrie GN, Balsevich G, Fuzesi T, Aukema RJ, Driever WPF, van der Stelt M, et al. Disruption of tonic endocannabinoid signalling triggers cellular, behavioural and neuroendocrine responses consistent with a stress response. *Br J Pharmacol*. 2023;180:3146–59.
156. Tanimura A, Yamazaki M, Hashimoto-dani Y, Uchigashima M, Kawata S, Abe M, et al. The endocannabinoid 2-arachidonoylglycerol produced by diacylglycerol lipase alpha mediates retrograde suppression of synaptic transmission. *Neuron*. 2010;65:320–7.
157. Barti B, Dudok B, Kenesei K, Zoldi M, Miczan V, Balla GY, et al. Presynaptic nanoscale components of retrograde synaptic signaling. *Sci Adv*. 2024;10:eado0077.
158. Bohme MA, McCarthy AW, Grasskamp AT, Beuschel CB, Goel P, Jusyte M, et al. Rapid active zone remodeling consolidates presynaptic potentiation. *Nat Commun*. 2019;10:1085.
159. Church E, Hamid E, Zurawski Z, Potcoava M, Flores-Barrera E, Caballero A, et al. Synaptic integration of subquantal neurotransmission by colocalized G protein-coupled receptors in presynaptic terminals. *J Neurosci*. 2022;42:980–1000.
160. Hruska M, Henderson N, Le Marchand SJ, Jafri H, Dalva MB. Synaptic nanomodules underlie the organization and plasticity of spine synapses. *Nat Neurosci*. 2018;21:671–82.
161. Newman ZL, Bakshinsky D, Schultz R, Kenny SJ, Moon S, Aghi K, et al. Determinants of synapse diversity revealed by super-resolution quantal transmission and active zone imaging. *Nat Commun*. 2022;13:229.
162. Caballero A, Flores-Barrera E, Cass DK, Tseng KY. Differential regulation of parvalbumin and calretinin interneurons in the prefrontal cortex during adolescence. *Brain Struct Funct*. 2014;219:395–406.
163. Tseng KY, O'Donnell P. Dopamine modulation of prefrontal cortical interneurons changes during adolescence. *Cereb Cortex*. 2007;17:1235–40.
164. Tseng KY, O'Donnell P. D2 dopamine receptors recruit a GABA component for their attenuation of excitatory synaptic transmission in the adult rat prefrontal cortex. *Synapse*. 2007;61:843–50.
165. Urs NM, Gee SM, Pack TF, McCory JD, Eron T, Snyder JC, et al. Distinct cortical and striatal actions of a beta-arrestin-biased dopamine D2 receptor ligand reveal unique antipsychotic-like properties. *Proc Natl Acad Sci USA*. 2016;113:E8178–E8186.

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## AUTHOR CONTRIBUTIONS

KYT and HM conceived and wrote the manuscript.

## COMPETING INTERESTS

The authors declare no competing interests.

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