psychoactives

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Review

Critical Windows of Vulnerability: Behavioral Dysregulation After Prenatal vs. Adolescent THC Exposure

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Abstract

This review synthesizes preclinical evidence on the behavioral and neurobiological effects of cannabis exposure during prenatal and adolescent developmental periods, with a focus on anxiety, social behavior, learning and memory, and associated brain changes. Understanding the differential impact of cannabis exposure across these windows is critical, given the increasing prevalence of cannabis use and the rising potency of its primary psychoactive component, delta-9-tetrahydrocannabinol (THC). Both prenatal and adolescent periods represent vulnerable windows for disruption of the endocannabinoid system, which plays a central role in typical neurodevelopment. Exogenous activation of this system via THC can lead to atypical brain maturation and subsequent behavioral impairments. These impairments are associated with region-specific alterations in cortical and subcortical structures and are highly dependent on the timing of exposure. For instance, prenatal exposure may disrupt medial prefrontal cortex development, leading to long-term social deficits while sparing memory function. In contrast, adolescent exposure tends to impair hippocampal function, resulting in learning and memory deficits. The manuscript is organized developmentally, beginning with the effects of prenatal exposure and then discussing consequences of adolescent exposure. By delineating the distinct behavioral and neurobiological outcomes associated with the timing of cannabis exposure, this review highlights the importance of developmental stage in assessing the risks of exogenous cannabinoid use and identifies critical periods for targeted research and intervention.

Keywords: THC; delta-9 tetrahydrocannabinol; prenatal; adolescence; learning and memory; social behaviors; substance use

Academic Editor: Ricardo Dinis-Oliveira

Received: 3 July 2025
Revised: 7 August 2025
Accepted: 8 August 2025
Published: 20 August 2025

Citation: Holliday, E.; Chowdhury, K.U.; Chen, K.; Saleem, B.; Yenduri, A.; Suppiramaniam, V. Critical Windows of Vulnerability: Behavioral Dysregulation After Prenatal vs. Adolescent THC Exposure. *Psychoactives* **2025**, *4*, 29. https://doi.org/10.3390/psychoactives4030029

1. Introduction

Cannabis use during pregnancy is on the rise due to perceived safety of cannabis use and compounded by legalization of recreational use in 24 states [1,2]. Unfortunately, there are documented consequences in children and adolescents exposed to cannabis in utero including emotional dysregulation [3], impaired attention [4], and impaired learning [5]. The prenatal period spans from conception to birth, lasting approximately 38 weeks in humans

and 20–21 days in rodents. In rodents, however, the first postnatal week developmentally aligns with the third trimester of gestation in humans [6]. The prenatal period is a critical window for brain development and susceptibility to deleterious maternal behaviors such as marijuana use. Current self-reports suggest 2–5% of pregnant women continue cannabis use during pregnancy (although it should be noted that usage reports jump to 20–30% for low-income, urban women [7], suggesting other factors that could mediate negative health outcomes). Together, this emphasizes a burgeoning public health crisis, and translational models using rodents with shorter gestational periods and shorter life spans can help us predict clinical outcomes resulting from prenatal stressors.

Adolescence is a developmental epoch characterized by common neurobiological changes that underlie some of the phenotypical behaviors displayed in adolescence [8]. Typical boundaries for adolescence include 12–18 years of age in humans and postnatal day (PND) 21–45 in rodents. For example, adolescence represents a time when the prefrontal cortex (PFC), which controls impulse control, is developing, but the limbic system, which controls motivation and reward seeking, is fully developed [9]. Thus, adolescents engage in more risky behaviors such as initiation of substance use and specifically cannabis use, with 29% of 12th graders reporting past-year use [10]. This mismatch sets a dangerous precedent where adolescents may experience strong perceived rewards from cannabis use without the accompanying negative withdrawal symptoms. This combination can result in intermittent use developing into compulsive use later in life due to adolescent insensitivity to aversive symptoms of substance use [11]. This pattern holds up across multiple classes of drugs including nicotine [12,13], alcohol [14,15], and opiates [16,17], where adolescents do not display similar levels of aversion, withdrawal severity, or anxiogenic effects compared to adults. This is true for Δ-9 tetrahyrdocannabinol (THC), the main psychoactive cannabinoid found in cannabis plants, where adolescents do not display similar locomotor depression effects or anxiogenesis during acute exposure. However, the long-term behavioral dysregulations resulting from adolescent cannabinoid activation are unique to this critical window. Thus, understanding differences in timing of cannabinoid exposure allows for improved policy changes and development of tailored personal interventions to alleviate the burden of developmental THC exposure.

2. Endocannabinoid System

The endocannabinoid system consists of the endogenous cannabinoids (eCBs), 2-arachidononyl glycerol (2-AG), and arachidonoyl ethanolamide (anandamide), being the two most studied examples that bind their cannabinoid receptor type-1 and type-2 (reviewed by [18]). The endogenous CBs are synthesized from precursors cleaved from plasma lipid membranes and released into the extracellular space. This synthesis pathway differs from classical neurotransmitters that are stored and released in synaptic vesicles. The prenatal and perinatal periods of development have high levels of endogenous cannabinoid activity, positioning both endogenous and exogenous cannabinoids as critical regulators of brain development. The endogenous CBs, AEA and 2-AG, are present in the developing brain during gestation, with levels of 2-AG at gestational day (GD) 21 comparable to adult levels, with a peak on the day after birth. AEA, on the other hand, increases expression during late adolescence and fluctuates before stabilizing in adulthood [19]. Furthermore, eCBs regulate synaptic plasticity, beginning at PND10, and activity increases into adolescence, demonstrating the role that the eCB system plays in typical neurodevelopment.

The cannabinoid (CB)1 receptor (CB1 receptor) is highly expressed in the central nervous system and signals through activation of G_i, ultimately decreasing intracellular cAMP [20]. Furthermore, CB1 mRNA expression is present in many white matter areas during fetal development that are not present in the adult brain, suggesting a role in axonal

guidance and corticolimbic circuitry development in early brain development [21]. The endocannabinoid system plays a role in brain development during the adolescent period, in addition to the prenatal periods. Overall expression of CB1-receptors and eCBs peaks during adolescence before decreasing and ultimately stabilizing in adulthood [22]. Notably, there may be fluctuations throughout adolescence, corresponding to the development of inhibitory systems within the PFC. CB1 receptor density also decreases from early to mid-adolescence and increases again from mid to late adolescence in the PFC, which was consistent for vehicle-treated and THC-exposed rats [23]. Furthermore, CB1 receptor density in the NAac shell shows THC exposure increases CB1 receptor density in early adolescence that does not persist into late adolescence [19].

Given the alterations in eCB system components (e.g., receptor location, eCB level changes) from prenatal to early adulthood, this positions both prenatal and adolescent THC exposure as a teratogen, impacting normal brain development. Considering the high density of CB1 receptors found in the corticolimbic structures, activation via exogenous cannabinoids, such as those in marijuana, including Δ-9 tetrahydrocannabinol (THC), alters the development of structures that regulate emotions as well as learning and memory. The introduction of exogenous THC in these critical windows of neurodevelopment causes long-lasting impacts on brain areas necessary for learning and memory, social behaviors, and affective behaviors. We have previously summarized the ways developmental cannabis exposure alters glutamatergic signaling, and this review extends our summary to focus on behavioral outcomes [24]. See Table 1. See Figure 1 for graphical representation.

Table 1. Summary of ages of exposure and behavioral outcomes. This table lists studies used in the review by time of cannabis exposure, time of behavioral experiments, and outcomes of behaviors. PND = postnatal day, IP = intraperitoneal, SC = subcutaneous.

Experiment	Time of Exposure to the Rodent Model	Drug and Dosage; Route of Administration	Age/Time Period of the Behavior Experiment	Outcome	Source or Reference
Ultrasonic-induced vocalization	GD 0–GD 21	400 mg/mL phytacannabinoid at a conc of 99.2 mg/mL THC; Vape	PND 6, PND 10, PND 13	Showed more frequency-modulated harmonic calls on P6 only	Weimer et al., 2020 [25]
Social Play behavior	GD 0–GD 21	400 mg/mL phytacannabinoid at a conc of 99.2 mg/mL THC; Vape	PND 26	Fewer social investigation cases on male only	Weimer et al., 2020 [25]
Elevated Plus Maze	GD 0–GD 21	400 mg/mL phytacannabinoid at a conc of 99.2 mg/mL THC; Vape	PND 27 (Adolescence) P73 (Adulthood)	No effect during adolescence, but increases anxiety-like behavior (spent less time exploring the open arms) during adulthood	Weimer et al., 2020 [25]
Behavioral Flexibility	GD 0–GD 21	99.2 mg/mL THC; Vape	PND 60–PND 110	Impaired	Weimer et al., 2020 [25]
					Miczek et al., 1979 [26]
		No THC, only aarachdonly 2-chloroethaylamide			Rodriguez-Arias et al., 2013 [27]

Table 1. *Cont.*

Experiment	Time of Exposure to the Rodent Model	Drug and Dosage; Route of Administration	Age/Time Period of the Behavior Experiment	Outcome	Source or Reference
Social Interaction test	E 10.5–E 18.5	0.75 mg/kg WIN55,212-2; IP	PND 14–PND 45	Decreased	Vargish, Pelkey, Yuan, Chittajallu, Collins, Fang, & McBain et al., 2017 [28]
Social Interaction test	GD 5–GD 20	0.5 mg/kg WIN; SC	PND > 90	Reduced sniffing, and playing behaviors are impaired, but the number of attacks remains unchanged (in males only)	Bara et al., 2018 [29]
Elevated Plus Maze	GD 5–GD 20	0.5 mg/kg WIN; SC	PND > 90	No differences	Bara et al., 2018 [29]
Elevated Plus Maze	GD 7–GD 22	3 mg/kg THC; IP	PND 35–PND 45	Increased anxiety-like behavior—Spent less time in open arms and more time in closed arms (in females only) Males spent more time in open arms and less time in closed arms	Devuono et al., 2024 [30]
Temporal Order Novel Object Recognition	GD 7–GD 22	3 mg/kg THC; IP	PND 35–PND 45	Impaired memory and reduced cognition (in males only)	Devuono et al., 2024 [30]
Three-Chamber Social interaction and Memory Test	GD 7–GD 22	3 mg/kg THC; IP	PND 35–PND 45	Reduced social recognition	Devuono et al., 2024 [30]
Open Field Test	GD 7–GD 22	3 mg/kg THC; IP	PND 35–PND 45	No Effect	Devuono et al., 2024 [30]
Pre Pulse Inhibition Test	GD 7–GD 22	3 mg/kg THC; IP	PND 35–PND 45	Sensorimotor gating impairments (in males only)	Devuono et al., 2024 [30]
Open Field Test	GD 5–GD 20	2 mg/kg THC; SC	PND 25 to PND 30	Increased locomotor activity	Brancato et al., 2020 [31]
Novel Object Recognition	GD 5–GD 20	2 mg/kg THC; SC	PND 25 to PND 30	No effect	Brancato et al., 2020 [31]
Enhanced Object Recognition	GD 5–GD 20	2 mg/kg THC; SC	PND 25 to PND 30	Decreased limbic learning and memory	Brancato et al., 2020 [31]
Barnes Maze	GD 5–GD 20	2 mg/kg Delta 9 THC; SC	PND 35–PND 46	Impaired retrieval and reversal	Castelli et al., 2023 [32]

Table 1. *Cont.*

Experiment	Time of Exposure to the Rodent Model	Drug and Dosage; Route of Administration	Age/Time Period of the Behavior Experiment	Outcome	Source or Reference
Can test	GD5–GD 20	2 mg/kg Delta 9 THC; SC	PND 35–PND 46	Impaired cognitive execution	Castelli et al., 2023 [32]
Barnes Maze	GD 5–GD 20	2 mg/kg Delta 9 THC; SC	PND 35–PND 60	Target latency increased in males only Prelocation and preservation errors (increased in male only) Retrieval delayed (in females only)	Castelli et al., 2024 [33]
Morris Water Maze (Visuospatial Learning)	GD 5–GD 20	100 mg/mL delta 9 THC; Vape	PND 40–PND 45	Impaired spatial learning and memory; required longer path lengths to find the hidden platform (in female only)	Lei et al., 2023 [34]
Morris Water Maze (Working Memory)	GD 5–GD 20	100 mg/mL delta 9 THC; Vape	PND 55–PND 60	No effect	Lei et al., 2023 [34]
Noble Object Recognition	G 0–G 20	5 mg/kg; Oral	PND 35	No preference for the noble object	Lallai et al., 2022 [35]
Novelty Suppressed Feeding Test	G 0–G 20 (preconception for five days)	5 mg/kg; Oral	PND 37	Longer approach latency (in males only)	Lallai et al., 2022 [35]
Open Field Test	GD 3-PND 2	2 mg/kg WIN 55,212; SC	PND 41	More time spent in the central area; decreased anxiety	Pinky et al., 2023 [36]
Contextual fear conditioning	GD 3-PND 2	2 mg/kg WIN 55,212; SC	PND 46–PND 47	Decreased freezing during contextual fear retention	Pinky et al., 2023 [36]
Morris Water Maze	GD 3-PND 2	2 mg/kg WIN 55,212; SC	PND 52–PND 53	Deficits in spatial memory	Pinky et al., 2023 [36]
Ultrasonic induced vocalization	GD 15-PND 9	2.5–5 mg/kg delta 9 THC; oral	PND 12	Increased number of ultrasounds	Trezza et al., 2008 [37]
Social Interaction	GD 15-PND 9	2.5–5 mg/kg delta 9 THC; oral	PND 35	Adolescents: ↓ social interaction/play	Trezza et al., 2008 [37]
Elevated Plus Maze	GD 15-PND 9	2.5–5 mg/kg delta 9 THC; oral	PND 80	Adults: anxiogenic-like profile in EPM (decreased time spent in open-arms)	Trezza et al., 2008 [37]
Open field	GD 1–GD 22, PND 2–PND 10	2 mg/kg delta 9 THC; SC	PND 90	Spent less time in inner zone, indicating increased anxiety-like behavior	Newsom et al., 2008 [38]

Table 1. *Cont.*

Experiment	Time of Exposure to the Rodent Model	Drug and Dosage; Route of Administration	Age/Time Period of the Behavior Experiment	Outcome	Source or Reference
Elevated Plus maze	GD 7–GD 22	3 mg/kg delta 9 THC; SC	PND 70–PND 100	Males spent less time in light/open arms; females unaffected	Sarikahya et al., 2022 [39]
Sucrose Preference test	GD 7–GD 22	3 mg/kg delta 9 THC; SC	PND 70–PND 100	No effect	Sarikahya et al., 2022 [39]
Object recognition memory	PND 28+ and PND 60+	5 mg/kg Delta 9 THC; IP	10–15 days washout and 17 days post last injection	Impaired only in adolescents	Quinn et al., 2008 [40]
	PND 28+ and PND 60+	5 mg/kg Delta 9 THC; IP	10–15 days washout and 17 days post last injection	Adults showed strong place aversion that persisted for 16 days; adolescents displayed no significant aversion; reduced social interaction in both groups	Quinn et al., 2008 [40]
Elevated Plus Maze	PND 35–45	2.5, 5, 10 mg/kg delta 9 THC; IP	PND 75	No change	Rubino et al., 2008 [41]
Open Field test	PND 35–45	2.5, 5, 10 mg/kg delta 9 THC; IP	PND 75	No change	Rubino et al., 2008 [41]
Forced Swim test	PND 35–45	2.5, 5, 10 mg/kg delta 9 THC; IP	PND 75	Adult females exhibited depressive-like behaviors in forced swim test (immobility ↑26%, climbing ↓40%) and anhedonia (↓ sucrose preference); males showed only anhedonia; reduced social interactions when tested in adulthood	Rubino et al., 2008 [41]
Elevated Plus Maze	PND 10–PND 16	10 mg/kg delta 9 THC; Oral	PND 37–PND 38	Males showed reduced anxiety-like behavior (increased open-arm time in elevated plus maze) and hyperactivity, but females did not	Mohammed et al., 2018 [42]

Table 1. *Cont.*

Experiment	Time of Exposure to the Rodent Model	Drug and Dosage; Route of Administration	Age/Time Period of the Behavior Experiment	Outcome	Source or Reference
Social Play Initiation	PND 10–PND 16	10 mg/kg delta 9 THC; Oral	PND 37–PND 38	Both sexes exhibited increased social play initiation	Mohammed et al., 2018 [42]
Social Interaction	PND 30–PND 43	5 mg/kg delta 9 THC; IP	PND 70	Reduced (in males only)	Mabou Tagne et al., 2021 [43]
Social interaction	PND 35–PND 56	10 mg/kg THC; IP	PND 70	Impaired	Zuo, Lemolo, Montilla-Perez, Li, Yang, & Telese et al., 2022 [44]
Elevated Plus Maze	PND 28–30 (Adolescent) PND 70+ (Adult)	0, 1, 5, or 10 mg/kg delta 9 THC, IP	PND 28–PND 30 (Adolescent) PND 70+ (Adult)	No change in adolescence but decreased open-arm entries in adulthood	Kasten et al., 2019 [45]
Noble Object Recognition	PND 28–30 (Adolescent) PND 70+ (Adult)	0, 1, 5, or 10 mg/kg delta 9 THC, IP	PND 28–PND 30 (Adolescent) PND 70+ (Adult)	No change	Kasten et al., 2019 [45]
					Chen and Mackie et al., 2020 [46]
					Harte-Hargrove and Dow-Edwards et al., 2012 [47]
	PND 35–PND 45	2.5, 5, 10 mg/kg Delta 9 THC; IP	PND 60+	Adult deficits in short-term memory, social motivation, and increased anxiety-like behavior—indicative of schizophrenia-like phenotypes	Renard et al., 2017 [48]
Open arm time	PND 21–PND 30 (F) PND 29–PND 28 (M)	3 mg/kg Delta 9 THC;IP		Pre-pubescent animals showed reduced anxiety (↑ open-arm time); effect absent in pubertal-treated animals	Silva et al., 2016 [49]
Noble object recognition	PND 35–PND 45	2.5, 5, 10 mg/kg delta 9 THC; IP	PND 75	Reduced (females only)	Prini et al., 2018 [50]
Social interaction	PND 35–PND 45	2.5, 5, 10 mg/kg delta 9 THC; IP	PND 75	Reduced (females only)	Prini et al., 2018 [50]
Conditioned Fear Cues	PND 35–PND 39	Delta 9 THC; Vapor	PND 60	Increased freezing	Smiley et al., 2021 [51]

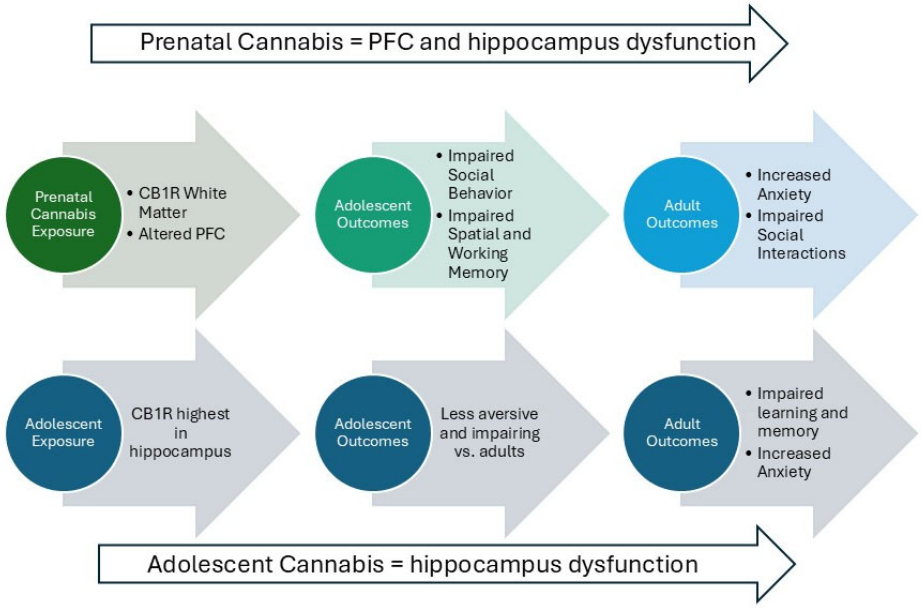

Figure 1. Graphical representation to demonstrate differences in behaviors between prenatal cannabis exposure (PCE) and adolescent cannabis exposure (ACE). Theoretical areas of the brain that are impacted by each window of vulnerability are noted in the arrows. Cannabis receptor 1 = CB1R.

3. Prenatal Exposure Adolescent Behaviors

Dosing pregnant dams with THC or analogs results in exposure to cannabinoids during gestation or during the prenatal period. The most common routes of administration are passive inhalation, oral gavage, and injection to the pregnant dam, which are passed on to prenatal pups. Some studies continue exposure during early perinatal periods so that cannabinoids pass through the milk ducts. Neonates exposed to CBs in utero exhibit increased ultrasonic vocalizations, decreased locomotor activity, and alterations in body weight [25]. However, many of the studies examining more complex behavioral outcomes of prenatal cannabis exposure (PCE) focus on behaviors in adolescence and are summarized below.

3.1. Social Interaction

The endocannabinoid system regulates both social behaviors and social reward in humans and rats, as evidenced by decreased aggression following THC and CB1 knockout mice exhibiting more aggressive behaviors [26,27]. Thus, alterations in eCB development due to exposure to exogenous cannabinoids result in alterations in social behaviors in adolescence. Adolescence in the rodent is characterized by increases in social play and social interaction that gradually wane into adulthood [52] and parallels the maturation of the PFC. Social behaviors during this time program appropriate social responses in adulthood, and impairments during adolescence can result in inappropriate threat evaluation, decreased social interaction, and increased anxiety in adulthood [53,54]. Prenatal THC exposure (400 mg/mL passive inhalation, final concentration at 99.2 mg/mL) resulted in less overall play behaviors and longer latencies to initiate contact with a conspecific age-matched control but had overall more pinning behaviors in adolescence. Males also had few social investigations compared to females [25]. Differences in social behaviors persist into adulthood with perinatally exposed rats (2 mg/kg, sc), displaying increased social exploration but coinciding with the inability to distinguish familiar vs. novel rats in the three-chamber social interaction test [30,55]. Together, these studies demonstrate that prenatal THC exposure impairs adolescent social behaviors that can develop into social anxiety and/or aggression later in life.

Notably, when WIN is used as the cannabis agonist, other studies report decreased social interaction in adult males following PCE [28,29]. These discrepancies may be explained by differences in intrinsic firing properties of cortical pyramidal neurons from the PFC elicited by WIN vs. THC, as THC appears to increase number of spikes, and sex-dependent alterations in membrane potentials in males vs. females [30]. ePCE also reduces eCB-mediated long-term depression (LTD) and increases excitability in layer V of the cortex, which may underlie the social behavior changes given that the PFC governs social behaviors, specifically the medial PFC (mPFC). It is a site for initiating social exploration and integrating social cues to initiate appropriate social responses.

3.2. Learning and Memory

Clinical studies consistently report impairments in attention, memory, and problem solving in children exposed to cannabis in utero [56]. Brain structures crucial to acquisition, consolidation, and retrieval of memories, such as the hippocampus and PFC, are modulated by eCBs and express high levels of CB1 receptors [57]. Programming of these areas begins in utero, and exposure to exogenous CBs alters normal hippocampus development, resulting in impaired learning and memory. Behavioral deficits are accompanied by decreases in crucial neuroplasticity proteins, including NPY [31], and PSD-95 [32,33] as well as a corresponding increase in CB1R mRNA and protein expression [30]. Thus, the cellular and molecular changes resulting from PCE at the level of the hippocampus correspond to observable deficits in associative learning, spatial memory, and working memory during adolescence and adulthood.

PCE impairs the retrieval of spatial memories assessed in the Barnes's Maze (2 mg/kg sc) [33]. Barne's Maze assesses the ability of rats to use external cues to navigate to an escape box on an open platform in mildly aversive conditions [58,59]. In addition to increasing latency to find the escape box, PCE significantly impaired flexibility of memory when the escape box was moved. Importantly, acquisition time to learn the location of the escape box was not significantly different from controls vs. PCE rats, indicating a deficit specific to consolidation and retrieval and not acquisition. These deficits were apparent in male but not female progeny [33]. Others have shown that adolescent rats exposed to PCE (100 mg/mL, inhalation) cannot recall the location of an escape platform in the Morris Water Maze (MWM) [34], a water-based spatial task similar to Barne's maze but with more aversion as rodents have to swim to the platform. This deficit was independent of differences in distance traveled in the maze and total distance traveled in an open-field test, indicating the inability to locate the escape platform was due to impaired recall of the spatial memory and not an overall decrease in mobility. A similar task, the Can task, uses appetitive reinforcement to learn the location of a water-rewarded can among non-rewarded cans, and revealed similar impairments in memory retrieval. Further, PCE rats showed decreased exploration when one of the cans was replaced with a novel object, indicating PCE may alter the development of the entorhinal cortex (object memory) and dorsal hippocampus (spatial memory) [33]. Males but not females demonstrate impaired temporal order novel object recognition compared to controls [30]. However, Lallai reported impairments in novel object discrimination in both males and females with a higher dose of THC (5 mg/kg vs. 3 mg/kg used by DeVeuono) [35]. In contrast to PCE with THC, PCE in the form of CBD does not impair spatial memory assessed in the Y-maze [60]. These findings suggest that PCE produces dose- and sex-dependent impairments in memory retrieval across multiple tasks assessing spatial, object, and temporal memory, likely through disruptions to hippocampal and entorhinal cortex function, while preserving memory acquisition.

3.3. Fear Conditioning

PCE likely alters the proper development and programming of all divisions of the hippocampus, given the abundance of CB1 receptor expression in the hippocampus and the role of eCB in modulating glutamatergic and GABAergic transmission. Adolescent rats exposed to PCE demonstrate lower freezing to a context previously associated with a mild foot shock, consistent with impaired memory consolidation and/or retrieval [36]. This study also found that prenatal exposure to cannabis compounds altered the expression of NMDA and AMPA receptor subunits, key components of glutamatergic signaling. These changes were accompanied by reduced expression of neural cell adhesion molecule (NCAM) and its polysialylated form (PSA-NCAM), which are critical for proper glutamate receptor function. Together, these molecular alterations impaired synaptic plasticity in the hippocampus. Consequently, PCE animals exhibited significant deficits in hippocampal-dependent behaviors, as demonstrated by contextual fear conditioning and Morris water maze performance.

In contrast, male offspring of WIN-infused dams demonstrate increased freezing in contextual fear conditioning. The authors point out this may be due to WIN altering maternal behaviors, as WIN-exposed rats display higher fear responses not only under fear conditioning but also from startle- and novelty-induced hypophagia, which is attenuated with higher maternal grooming behaviors [61]. Thus, future studies should examine the interaction of early life stress and substance use to better understand the development of altered fear expression as well as including measures on maternal care behaviors following PCE.

3.4. Anxiety

Increased anxiety is reported in children exposed to THC in utero [62,63]. However, preclinical studies suggest that while PCE increases anxiety-like behaviors, this phenotype does not emerge until adulthood. For example, PCE did not alter anxiety measured in the EPM in male and female adolescent rats [30,64] as well as in female pre-adolescent rats [65]. These findings are supported by others reporting no changes reported in pre-adolescent (PND 24–28) PCE (2 mg/kg, sc) vs. control rats in time spent in the center of an open field arena [65]. In a study using passive inhalation for PCE, no differences in total distance traveled were observed, but PCE did decrease the amount of time spent in the center arena of an open field apparatus, an indicator of anxiogenic behavior [36] in late adolescent rats (PND 41). This highlights the importance of considering not only the age when behavioral experiments start but also the route of administration when presented with different findings.

The increased anxiety in late adolescence is in line with other studies examining anxiety measures conducted in PCE adult rats. For example, adult Wistar rats exposed to PCE demonstrate significantly reduced time in the open arms of EPM at the highest dose [37]. Weimer et al. reported more anxiety-like behavior with decreased exploration of open arms in adult rats (PND 73) following PCE, utilizing an inhalation delivery of THC, as well as no changes in anxiety when EPM tested at PND 21. Furthermore, center time in the open field arena was significantly reduced at PND 90 following PCE (2 mg/kg, 2 × a day, sc) in male Long-Evans [38]. Studies utilizing light–dark box to assess anxiety also report increased anxiety in adult male rats but not in females following PCE, and persisted with EPM reports [39]. Thus, while increased anxiety is not a characteristic of PCE adolescents, it does increase anxiety in adult PCE animals. This suggests long-term epigenetic modulation via PCE, possibly in the amygdala and hypothalamus–pituitiary–adrenal axis that are masked in adolescence and unmasked in adulthood. Future work should determine the unique role of PCE in programming adult behaviors that are spared during adolescence.

4. Adolescent Exposure

Adolescent use of cannabis self-reports has remained stable since 2020, with around 30% of 12th graders reporting use within the last 12 months [10]. However, more alarming is the rise in potency in available products as heavy marijuana use is correlated to an increased risk for the onset of psychosis [66]. Here we describe the outcomes of THC exposure during adolescence and adulthood.

4.1. Social Interaction

As mentioned previously, adolescence is the peak for social behaviors that program the PFC for integrating social cues and executing appropriate social responses. Social interactions are decreased following an acute activation of eCB [37] and following drug washout in late adolescence and adulthood. Quinn et al. found that following THC administration starting at PND32 for 18 days resulted in lowered social behaviors and when tested 15 days after the last drug exposure, but did not significantly reduce total social interaction following an acute exposure of THC [40]. The same pattern was observed for adult rats on the same treatment course but starting THC exposure in adulthood. Female rats were subjected to increasing doses of THC (2.5 mg/kg, 5 mg/kg, 10 mg/kg), with twice-daily injections for 10 days to model heavy cannabis use displaying reduced social interactions when tested in adulthood (PND 75) [41]. When focusing on specific play behaviors vs. total social interaction, chronic THC administration (5 mg/kg, 14 days) resulted in decreased number of attacks, pins, and defensive behaviors in both male and female. Interestingly, when repeated THC dosing occurred in periadolescence, it resulted in increased active social behaviors but decreased social exploration. This indicates earlier timing of THC, like with prenatal dosing, alters social interactions likely through alterations in the developmental timeline of the PFC [42].

However, mice exposure to 3 mg/kg of THC for three weeks in adolescence did not result in impaired social interaction in adulthood. Adolescent THC exposure did not alter adult social behaviors in mice but did decrease social interactions following a formalin injection to simulate chronic pain [43]. A high-exposure dosing regimen of THC (10 mg/kg, once a day, 21 days) resulted in impaired social interaction in both male and female mice when tested in late adolescence [44]. Thus, sex, species, and dosing likely alter the phenotypical behaviors, and future studies should include wider dose ranges specific to social behaviors.

4.2. Learning and Memory

Clinical findings report adolescent cannabis use is associated with deficits in cognitive function, such as verbal and working memory, sustained attention, and executive functioning [67]. Adolescent THC exposure impairs some types of memory while sparing others. Activation of CB1 receptors in the dorsal hippocampus impairs the ability to discriminate a novel object from a familiar object in adult rats [68]. However, acute THC did not alter object recognition memory in early adolescent C57B6 mice, nor did it induce anxiety in the EPM [45]. Acute THC in adolescent rats (PND 30) did not impair novel object recognition but did impair novelty discrimination in adults. Thus, acute psychoactive impairments of THC may be diminished in adolescents vs. adults, leading to repeated use and increasing the likelihood of long-term consequences. In fact, Zuo et al. show impaired object recognition following heavy cannabis exposure in late adolescence and novelty exploration was reduced only in females [44]. In support, Prini et al. (2018) found impaired novel object discrimination in adult female rats following heavy cannabis exposure in adolescence. Impairments in object recognition were accompanied by decreased social behaviors and increased immobility and decreased swimming consistent with a phenotype of depres-

sion [50]. Increased markers of transcriptional repression and decreased expression of synaptic plasticity genes likely underlie the persistent alterations seen following adolescent THC exposure but not adult THC exposure, substantiating the idea that adolescence is a critical window of vulnerability for long-lasting consequences from cannabis use specific to hippocampus signaling.

4.3. Fear Conditioning

Recalling the environment in which an aversive stimulus is applied requires an intact hippocampus, and lower freezing to the context implies deficient hippocampus processing [69]. WIN administration to adult Wistar rats impaired contextual fear memories but did not cue illicted freezing [70], likely due to the high concentration of CB1 receptors, and in fact, CB1 receptor agonists have been explored as treatment for persistent traumatic memory recall like that observed in PTSD. Lightfoot et al. (2025) extend these findings to adolescent THC exposure and reported that acute THC exposure does not impair acquisition of fear memories in male and female rats but does impair recall in females only [71]. Acute cannabis also facilitated faster extinction in males while impairing extinction in females. Chronic THC did not alter long-term fear memories, as spontaneous recovery was not impaired.

Notably, mice receiving 8 mg/kg per day for 21 days starting at PND 21 did not display deficits in fear conditioning when tested 20 days after last exposure [72]. Specifically, mice displayed similar levels of freezing to a context previously paired with a foot shock, which is a hippocampus-dependent behavior. In contrast, THC administration beginning in late adolescence enhanced freezing 14 days after the last THC administration to the conditioned stimulus and acquired conditioning significantly sooner compared to control conditions [51]. Interestingly, CB1 receptor knockout mice display enhanced fear conditioning, suggesting the eCB system helps attenuate emotional memories with aversive stimuli [73]. These disparate results suggest acute CB1 receptor agonism during adolescence modulates hippocampus-independent memory mechanisms more profoundly and results in long-term alterations in hippocampus-dependent mechanisms that are present later in life.

Together, this suggests the impact of CB1 receptor activation may induce epigenetic changes that are not apparent following acute administration in adolescence. Timing of THC exposure needs to be considered when discussing impacts on learning and memory, as acute, chronic, and protracted withdrawal create disparate findings, with protracted withdrawal from chronic exposure during prenatal or adolescent periods creating the most pronounced deficits.

4.4. Anxiety

Adolescent cannabis use exacerbates anxiety symptoms, and adolescent cannabis use can be a risk factor for the development of anxiety disorders later in life [74]. Preclinical studies partially support these clinical findings as increased anxiety measures may be age-dependent and task-specific. For example, acute THC did not alter EPM behaviors relative to controls in adolescent male or female mice but did decrease time in open arms for both sexes when treated in adulthood [45]. In contrast, chronic THC exposure (3 mg/kg) during adolescence did not induce anxiety when tested in adulthood at PND 76 in C57B6 mice. Interestingly, this same dosing paradigm resulted in impaired working memory while not impacting social behaviors when tested in adulthood [46]. Furthermore, one day of abstinence from a high or lose dose of THC decreased time spent in open arms in female Sprague-Dawleys while increasing time spent in the open arms in males at the highest dose tested [47]. There were no differences in anxiety following a 2 week drug washout period,

again suggesting the long-term impairments from adolescent THC are specific to learning and memory measures (reviewed in the following section) but not in anxiety-related behaviors [47]. However, when using the light–dark box, Renard et al. found significant increases in latency to transition from dark side to light side [48]. Hyperexcitability of pyramidal cells in the PFC likely underlie these changes as GABA agonists reverse these impairments [48]. Decreased anxiety occurs following a period of protracted abstinence and when THC is dosed during prepubertal ages (P21–P30), as there were no changes in anxiety following adolescent dosing [49]. Furthermore, a low dose of THC given for 20 days during mid to late adolescence increased anxiety following a 20 day protracted abstinence that was also seen in adults given the same treatment [75]. Increased anxiety extends to the novelty feeding suppression test (NFST) test, with increased latency to start feeding but no differences in latency to approach food in adult rats administered THC in adolescence. These studies emphasize cannabinoids as potent regulators of behavioral phenotypes associated with psychiatric illness and epigenetic regulation in cortical and limbic areas of the brain. Like with PCE, adolescent THC does not result in immediate alterations in anxiety but increases anxiety measures when tested following protracted abstinence. Differences in anxiogenic responses could be due to alterations in CB1 localization on GABAergic vs. glutamatergic neurons.

5. Discussion

Prenatal cannabis exposure and adolescent cannabis exposure represent two disparate developmental windows that lead to divergent outcomes. Specifically, PCE results in impairments in social interactions in adolescence as well as in working and spatial memory. PCE also increases anxiety in adulthood, and these increases are absent during the adolescent window. On the other hand, adolescent exposure to cannabis results in increased anxiety in adulthood but not during adolescence. Adolescents are also less sensitive to the acute cognitive deficits, social impairments, and anxiogenic effects of cannabis exposure. However, chronic exposure followed by protracted abstinence results in marked increases in anxiety and significant impairments in learning and memory. Collectively, these findings suggest the endocannabinoid system modulates neurodevelopment of the PFC during gestation and the hippocampus during adolescence.

Animal models have demonstrated that disrupting endocannabinoid (eCB) signaling during prenatal and adolescent periods yields persistent alterations in social behavior, learning and memory, emotional regulation, and motivated behaviors. For instance, prenatal THC exposure in rats leads to reduced social play, delayed spatial memory retrieval in the Barnes Maze, and blunted contextual fear conditioning in adolescence, and these effects often persist into adulthood [25,33]. At the synaptic level, these behavioral deficits are underpinned by CB_1-dependent disruptions of glutamatergic presynaptic machinery, such as increased VGLUT1/2 expression [76], inhibition of N- and P/Q-type calcium channels [77,78], and downregulation of synaptic proteins in the medial prefrontal cortex [31,33]. Adolescent THC exposure likewise produces sex- and dose-dependent social impairments, object recognition deficits, and altered extinction of conditioned fear, reflecting a disruption of PFC and hippocampal circuits during a period of heightened eCB-mediated synaptic pruning and plasticity [41,43,44,71].

In humans, prenatal cannabis exposure (PCE) is associated with obstetric risks, including low birth weight, preterm birth, and increased NICU admissions, as well as subtle neurobehavioral changes in early childhood. Meta-analyses indicate that PCE increases attention problems and externalizing behaviors in toddlers, although gross cognitive impairments are less consistently observed after adjusting for confounders such as socioeconomic status and polydrug use [79,80]. Longitudinal data from large cohorts (e.g., the Adolescent

Brain Cognitive Development Study, ABCD) show that by ages 9–11, children with PCE perform similarly to controls on most cognitive tasks once covariates are accounted for, although small deficits in visuospatial processing and intracranial volume trajectories can emerge [4,56]. Functional imaging studies implicate altered PFC–hippocampal connectivity in adolescent users, similar to the synaptic and circuit-level disruptions seen in animal ACE paradigms [81,82]. Adolescent cannabis use in human cohorts mirrors many rodent findings: heavy, early-onset use correlates with modest but significant reductions in executive function, attention, working memory, and verbal learning, some of which partially recover with abstinence [83,84]. However, this is not in line with rodent studies that demonstrate impairments following periods of protracted abstinence. These differences may be related to environmental enrichment in humans and/or intrinsic motivation to stop cannabis use, and future clinical studies should consider including characterizing behaviors and other environmental factors during abstinence.

6. Conclusions

Overall, the translational parallels are striking and gives credibility to the external validity of preclinical maternal stress and maternal cannabis use models to study the long-lasting impacts on both mother and child. In rodents, prenatal and adolescent THC exposures produce robust hippocampal-dependent learning deficits, social behavior impairments, and anxiety-like phenotypes that correspond to domain-specific attentional and externalizing problems in human offspring after PCE [25,32,79]. Similarly, adolescent cannabis exposure in rodents disrupts social interaction, object recognition, and fear extinction in a sex-dependent manner, paralleling small but measurable executive and memory deficits observed in human adolescents with heavy cannabis use [48,83,84] Together, these findings suggest the endocannbinoid system modulates the neurodevelopment of the prefrontal cortex during gestation and, in contrast, the hippocampus during adolescence. Future studies should also incorporate cannabis use trajectories to include both PCE and adolescent cannabis exposure in the experimental design to further improve translational validity [85]. These convergent findings underscore that critical developmental windows such as prenatal and adolescence are especially vulnerable to exogenous cannabinoids, and they reinforce the need for public health measures aimed at minimizing cannabis exposure during these sensitive periods.

Author Contributions: Conceptualization, E.H. and K.U.C.; methodology, E.H., K.U.C. and B.S.; writing—original draft preparation, E.H.; writing—review and editing, E.H., K.U.C., B.S., K.C., A.Y. and V.S.; supervision, E.H. and V.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by NIH NIDA grant number "5R01DA046723-02" and The Kennesaw State Office of Research and the Radow College of Humanities and Social Sciences.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Thompson, R.; DeJong, K.; Lo, J. Marijuana Use in Pregnancy: A Review. *Obstet. Gynecol. Surv.* **2019**, *74*, 415–428. [CrossRef]
2. Bryan, K. Cannabis Overview, National Conference of State Legislatures. Available online: https://www.ncsl.org/civil-and-criminal-justice/cannabis-overview (accessed on 19 September 2024).
3. Goldschmidt, L.; Day, N.L.; Richardson, G.A. Effects of prenatal marijuana exposure on child behavior problems at age 10. *Neurotoxicol. Teratol.* **2000**, *22*, 325–336. [CrossRef]
4. Paul, S.E.; Hatoum, A.S.; Fine, J.D.; Johnson, E.C.; Hansen, I.; Karcher, N.R.; Moreau, A.L.; Bondy, E.; Qu, Y.; Carter, E.B.; et al. Associations Between Prenatal Cannabis Exposure and Childhood Outcomes: Results From the ABCD Study. *JAMA Psychiatry* **2021**, *78*, 64–76. [CrossRef] [PubMed]

5. Moore, B.F.; Salmons, K.A.; Hoyt, A.T.; Swenson, K.S.; Bates, E.A.; Sauder, K.A.; Shapiro, A.L.B.; Wilkening, G.; Kinney, G.L.; Neophytou, A.M.; et al. Associations between Prenatal and Postnatal Exposure to Cannabis with Cognition and Behavior at Age 5 Years: The Healthy Start Study. *Int. J. Environ. Res. Public Health* **2023**, *20*, 4880. [CrossRef] [PubMed]
6. Aguilera, N.; Salas-Pérez, F.; Ortíz, M.; Álvarez, D.; Echiburú, B.; Maliqueo, M. Rodent models in placental research. Implications for fetal origins of adult disease. *Anim. Reprod.* **2022**, *19*, e20210134. [CrossRef]
7. Committee Opinion Marijuana Use During Pregnancy and Lactation. Available online: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/10/marijuana-use-during-pregnancy-and-lactation (accessed on 19 September 2024).
8. Spear, L.P. The adolescent brain and age-related behavioral manifestations. *Neurosci. Biobehav. Rev.* **2000**, *24*, 417–463. [CrossRef]
9. Arain, M.; Haque, M.; Johal, L.; Mathur, P.; Nel, W.; Rais, A.; Sandhu, R.; Sharma, S. Maturation of the adolescent brain. *Neuropsychiatr. Dis. Treat.* **2013**, *9*, 449–461. [CrossRef] [PubMed]
10. Miech, R.A.; Johnston, L.D.; Patrick, M.E.; O'Malley, P. *Monitoring the Future National Survey Results on Drug Use, 1975–2024: Overview and Detailed Results for Secondary School Students*; Institute for Social Research, University of Michigan: Ann Arbor, MI, USA, 2025; Available online: https://monitoringthefuture.org/results/annual-reports/ (accessed on 20 June 2025).
11. Bjork, J.M. The Ups and Downs of Relating Nondrug Reward Activation to Substance Use Risk in Adolescents. *Curr. Addict. Rep.* **2020**, *7*, 421–429. [CrossRef]
12. Holliday, E.D.; Logue, S.F.; Oliver, C.; Bangasser, D.A.; Gould, T.J. Stress and nicotine during adolescence disrupts adult hippocampal-dependent learning and alters stress reactivity. *Addict. Biol.* **2019**, *25*, e12769. [CrossRef]
13. Portugal, G.S.; Wilkinson, D.S.; Turner, J.R.; Blendy, J.A.; Gould, T.J. Developmental effects of acute, chronic, and withdrawal from chronic nicotine on fear conditioning. *Neurobiol. Learn. Mem.* **2012**, *97*, 482–494. [CrossRef]
14. Logue, S.; Chein, J.; Gould, T.; Holliday, E.; Steinberg, L. Adolescent mice, unlike adults, consume more alcohol in the presence of peers than alone. *Dev. Sci.* **2014**, *17*, 79–85. [CrossRef]
15. Spear, L.P. Adolescents and alcohol: Acute sensitivities, enhanced intake, and later consequences. *Neurotoxicol. Teratol.* **2014**, *41*, 51–59. [CrossRef]
16. Doherty, J.M.; Frantz, K.J. Heroin self-administration and reinstatement of heroin-seeking in adolescent vs. adult male rats. *Psychopharmacology* **2012**, *219*, 763–773. [CrossRef]
17. Zhang, Y.; Picetti, R.; Butelman, E.R.; Schlussman, S.D.; Ho, A.; Kreek, M.J. Behavioral and Neurochemical Changes Induced by Oxycodone Differ Between Adolescent and Adult Mice. *Neuropsychopharmacology* **2009**, *34*, 912–922. [CrossRef] [PubMed]
18. Lu, H.-C.; Mackie, K. An introduction to the endogenous cannabinoid system. *Biol. Psychiatry* **2016**, *79*, 516–525. [CrossRef]
19. Ellgren, M.; Artmann, A.; Tkalych, O.; Gupta, A.; Hansen, H.S.; Hansen, S.H.; Devi, L.A.; Hurd, Y.L. Dynamic changes of the endogenous cannabinoid and opioid mesocorticolimbic systems during adolescence: THC effects. *Eur. Neuropsychopharmacol.* **2008**, *18*, 826–834. [CrossRef] [PubMed]
20. Demuth, D.G.; Molleman, A. Cannabinoid signalling. *Life Sci.* **2006**, *78*, 549–563. [CrossRef] [PubMed]
21. Gómez, M.; Hernández, M.L.; Pazos, M.R.; Tolón, R.M.; Romero, J.; Fernández-Ruiz, J. Colocalization of CB1 receptors with L1 and GAP-43 in forebrain white matter regions during fetal rat brain development: Evidence for a role of these receptors in axonal growth and guidance. *Neuroscience* **2008**, *153*, 687–699. [CrossRef]
22. Heng, L.; Beverley, J.A.; Steiner, H.; Tseng, K.Y. Differential developmental trajectories for CB1 cannabinoid receptor expression in limbic/associative and sensorimotor cortical areas. *Synapse* **2011**, *65*, 278–286. [CrossRef]
23. Schneider, M. Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. *Addict. Biol.* **2008**, *13*, 253–263. [CrossRef]
24. Chowdhury, K.U.; Holden, M.E.; Wiley, M.T.; Suppiramaniam, V.; Reed, M.N. Effects of Cannabis on Glutamatergic Neurotransmission: The Interplay between Cannabinoids and Glutamate. *Cells* **2024**, *13*, 1130. [CrossRef]
25. Weimar, H.V.; Wright, H.R.; Warrick, C.R.; Brown, A.M.; Lugo, J.M.; Freels, T.G.; McLaughlin, R.J. Long-term effects of maternal cannabis vapor exposure on emotional reactivity, social behavior, and behavioral flexibility in offspring. *Neuropharmacology* **2020**, *179*, 108288. [CrossRef]
26. Miczek, K. Chronic Δ9-Tetrahydrocannabinol in rats: Effect on social interactions, mouse killing, motor activity, consummatory behavior, and body temperature. *Psychopharmacology* **1979**, *60*, 137–146. [CrossRef] [PubMed]
27. Rodriguez-Arias, M.; Navarrete, F.; Daza-Losada, M.; Navarro, D.; Aguilar, M.A.; Berbel, P.; Miñarro, J.; Manzanares, J. CB1 cannabinoid receptor-mediated aggressive behavior. *Neuropharmacology* **2013**, *75*, 172–180. [CrossRef] [PubMed]
28. Vargish, G.A.; Pelkey, K.A.; Yuan, X.; Chittajallu, R.; Collins, D.; Fang, C.; McBain, C.J. Persistent inhibitory circuit defects and disrupted social behaviour following in utero exogenous cannabinoid exposure. *Mol. Psychiatry* **2017**, *22*, 56–67. [CrossRef]
29. Bara, A.; Manduca, A.; Bernabeu, A.; Borsoi, M.; Serviado, M.; Lassalle, O.; Murphy, M.; Wager-Miller, J.; Mackie, K.; Pelissier-Alicot, A.-L.; et al. Sex-dependent effects of in utero cannabinoid exposure on cortical function. *Elife* **2018**, *7*, e36234. [CrossRef]
30. DeVuono, M.V.; Nashed, M.G.; Sarikahya, M.H.; Kocsis, A.; Lee, K.; Vanin, S.R.; Hudson, R.; Lonnee, E.P.; Rushlow, W.J.; Hardy, D.B.; et al. Prenatal tetrahydrocannabinol and cannabidiol exposure produce sex-specific pathophysiological phenotypes in the adolescent prefrontal cortex and hippocampus. *Neurobiol. Dis.* **2024**, *199*, 106588. [CrossRef]

31. Brancato, A.; Castelli, V.; Lavanco, G.; Marino, R.A.M.; Cannizzaro, C. In utero Δ9-tetrahydrocannabinol exposure confers vulnerability towards cognitive impairments and alcohol drinking in the adolescent offspring: Is there a role for neuropeptide Y? *J. Psychopharmacol.* **2020**, *34*, 663–679. [CrossRef]
32. Castelli, V.; Lavanco, G.; Feo, S.; D'Amico, C.; Micale, V.; Kuchar, M.; Plescia, F.; Brancato, A.; Cannizzaro, C. Prenatal Exposure to Δ9-Tetrahydrocannabinol Affects Hippocampus-Related Cognitive Functions in the Adolescent Rat Offspring: Focus on Specific Markers of Neuroplasticity. *Pharmaceutics* **2023**, *15*, 692. [CrossRef]
33. Castelli, V.; Lavanco, G.; Tringali, G.; D'Amico, C.; Feo, S.; Di Bartolomeo, M.; D'Addario, C.; Kuchar, M.; Brancato, A.; Cannizzaro, C. Prenatal THC exposure drives sex-specific alterations in spatial memory and hippocampal excitatory/inhibitory balance in adolescent rats. *Biomed. Pharmacother.* **2024**, *181*, 117699. [CrossRef] [PubMed]
34. Lei, A.; Breit, K.R.; Thomas, J.D. Prenatal alcohol and tetrahydrocannabinol exposure: Effects on spatial and working memory. *Front. Neurosci.* **2023**, *17*, 1192786. [CrossRef]
35. Lallai, V.; Manca, L.; Sherafat, Y.; Fowler, C.D. Effects of Prenatal Nicotine, THC, or Co-Exposure on Cognitive Behaviors in Adolescent Male and Female Rats. *Nicotine Tob. Res.* **2022**, *24*, 1150–1160. [CrossRef]
36. Pinky, P.D.; Bloemer, J.; Smith, W.D.; Du, Y.; Heslin, R.T.; Setti, S.E.; Pfitzer, J.C.; Chowdhury, K.; Hong, H.; Bhattacharya, S.; et al. Prenatal Cannabinoid Exposure Elicits Memory Deficits Associated with Reduced PSA-NCAM Expression, Altered Glutamatergic Signaling, and Adaptations in Hippocampal Synaptic Plasticity. *Cells* **2023**, *12*, 2525. [CrossRef]
37. Trezza, V.; Campolongo, P.; Cassano, T.; Macheda, T.; Dipasquale, P.; Carratù, M.R.; Gaetani, S.; Cuomo, V. Effects of perinatal exposure to delta-9-tetrahydrocannabinol on the emotional reactivity of the offspring: A longitudinal behavioral study in Wistar rats. *Psychopharmacology* **2008**, *198*, 529–537. [CrossRef] [PubMed]
38. Newsom, R.J.; Kelly, S.J. Perinatal delta-9-tetrahydrocannabinol exposure disrupts social and open field behavior in adult male rats. *Neurotoxicol. Teratol.* **2008**, *30*, 213–219. [CrossRef]
39. Sarikahya, M.H.; Cousineau, S.; Felice, M.D.; Lee, K.; Wong, K.K.; DeVuono, M.V.; Jung, T.; Rodríguez-Ruiz, M.; Ng, T.H.J.; Gummerson, D.; et al. Prenatal THC Exposure Induces Sex-Dependent Neuropsychiatric Endophenotypes in Offspring and Long-Term Disruptions in Fatty-Acid Signaling Pathways Directly in the Mesolimbic Circuitry. *Eneuro* **2022**, *9*, 1–16. [CrossRef] [PubMed]
40. Quinn, H.R.; Matsumoto, I.; Callaghan, P.D.; Long, L.E.; Arnold, J.C.; Gunasekaran, N.; Thompson, M.R.; Dawson, B.; Mallet, P.E.; Kashem, M.A.; et al. Adolescent Rats Find Repeated Δ9-THC Less Aversive Than Adult Rats but Display Greater Residual Cognitive Deficits and Changes in Hippocampal Protein Expression Following Exposure. *Neuropsychopharmacology* **2008**, *33*, 1113–1126. [CrossRef]
41. Rubino, T.; Vigano', D.; Realini, N.; Guidali, C.; Braida, D.; Capurro, V.; Castiglioni, C.; Cherubino, F.; Romualdi, P.; Candeletti, S.; et al. Chronic Δ9-Tetrahydrocannabinol During Adolescence Provokes Sex-Dependent Changes in the Emotional Profile in Adult Rats: Behavioral and Biochemical Correlates. *Neuropsychopharmacology* **2008**, *33*, 2760–2771. [CrossRef]
42. Mohammed, A.N.; Alugubelly, N.; Kaplan, B.L.; Carr, R.L. Effect of repeated juvenile exposure to Δ9-tetrahydrocannabinol on anxiety-related behavior and social interactions in adolescent rats. *Neurotoxicol. Teratol.* **2018**, *69*, 11–20. [CrossRef]
43. Mabou Tagne, A.; Fotio, Y.; Alan Springs, Z.; Su, S.; Piomelli, D. Frequent Δ9- tetrahydrocannabinol exposure during adolescence impairs sociability in adult mice exposed to an aversive painful stimulus. *Eur. Neuropsychopharmacol.* **2021**, *53*, 19–24. [CrossRef] [PubMed]
44. Zuo, Y.; Iemolo, A.; Montilla-Perez, P.; Li, H.-R.; Yang, X.; Telese, F. Chronic adolescent exposure to cannabis in mice leads to sex-biased changes in gene expression networks across brain regions. *Neuropsychopharmacology* **2022**, *47*, 2071–2080. [CrossRef]
45. Kasten, C.R.; Zhang, Y.; Boehm, S.L. Acute Cannabinoids Produce Robust Anxiety-Like and Locomotor Effects in Mice, but Long-Term Consequences Are Age- and Sex-Dependent. *Front. Behav. Neurosci.* **2019**, *13*, 32. [CrossRef]
46. Chen, H.-T.; Mackie, K. Adolescent Δ9-Tetrahydrocannabinol Exposure Selectively Impairs Working Memory but Not Several Other mPFC-Mediated Behaviors. *Front. Psychiatry* **2020**, *11*, 576214. [CrossRef] [PubMed]
47. Harte-Hargrove, L.C.; Dow-Edwards, D.L. Withdrawal from THC during Adolescence: Sex Differences in Locomotor Activity and Anxiety. *Behav. Brain Res.* **2012**, *231*, 48–59. [CrossRef] [PubMed]
48. Renard, J.; Szkudlarek, H.J.; Kramar, C.P.; Jobson, C.E.L.; Moura, K.; Rushlow, W.J.; Laviolette, S.R. Adolescent THC Exposure Causes Enduring Prefrontal Cortical Disruption of GABAergic Inhibition and Dysregulation of Sub-Cortical Dopamine Function. *Sci. Rep.* **2017**, *7*, 11420. [CrossRef] [PubMed]
49. Silva, L.; Black, R.; Michaelides, M.; Hurd, Y.L.; Dow-Edwards, D. Sex and age specific effects of delta-9-tetrahydrocannabinol during the periadolescent period in the rat: The unique susceptibility of the prepubescent animal. *Neurotoxicol. Teratol.* **2016**, *58*, 88–100. [CrossRef]
50. Prini, P.; Rusconi, F.; Zamberletti, E.; Gabaglio, M.; Penna, F.; Fasano, M.; Battaglioli, E.; Parolaro, D.; Rubino, T. Adolescent THC exposure in female rats leads to cognitive deficits through a mechanism involving chromatin modifications in the prefrontal cortex. *J. Psychiatry Neurosci.* **2018**, *43*, 87–101. [CrossRef]

51. Smiley, C.E.; Saleh, H.K.; Nimchuk, K.E.; Garcia-Keller, C.; Gass, J.T. Adolescent exposure to delta-9-tetrahydrocannabinol and ethanol heightens sensitivity to fear stimuli. *Behav. Brain Res.* **2021**, *415*, 113517. [CrossRef]
52. Panksepp, J.; Siviy, S.; Normansell, L. The psychobiology of play: Theoretical and methodological perspectives. *Neurosci. Biobehav. Rev.* **1984**, *8*, 465–492. [CrossRef]
53. Green, M.R.; Barnes, B.; McCormick, C.M. Social instability stress in adolescence increases anxiety and reduces social interactions in adulthood in male long–evans rats. *Dev. Psychobiol.* **2013**, *55*, 849–859. [CrossRef]
54. Orben, A.; Tomova, L.; Blakemore, S.-J. The effects of social deprivation on adolescent development and mental health. *Lancet Child Adolesc. Health* **2020**, *4*, 634–640. [CrossRef] [PubMed]
55. Scheyer, A.F.; Laviolette, S.R.; Pelissier, A.-L.; Manzoni, O.J.J. Cannabis in Adolescence: Lasting Cognitive Alterations and Underlying Mechanisms. *Cannabis Cannabinoid Res.* **2023**, *8*, 12–23. [CrossRef] [PubMed]
56. Sharapova, S.R.; Phillips, E.; Sirocco, K.; Kaminski, J.W.; Leeb, R.T.; Rolle, I. Effects of prenatal marijuana exposure on neuropsychological outcomes in children aged 1–11 years: A systematic review. *Paediatr. Perinat. Epidemiol.* **2018**, *32*, 512–532. [CrossRef]
57. Matsuda, L.A.; Bonner, T.I.; Lolait, S.J. Localization of cannabinoid receptor mRNA in rat brain. *J. Comp. Neurol.* **1993**, *327*, 535–550. [CrossRef]
58. Barnes, C.A. Memory deficits associated with senescence: A neurophysiological and behavioral study in the rat. *J. Comp. Physiol. Psychol.* **1979**, *93*, 74–104. [CrossRef]
59. Pitts, M.W. Barnes Maze Procedure for Spatial Learning and Memory in Mice. *Bio Protoc.* **2018**, *8*, e2744. [CrossRef]
60. Swenson, K.S.; Gomez Wulschner, L.E.; Hoelscher, V.M.; Folts, L.; Korth, K.M.; Oh, W.C.; Bates, E.A. Fetal cannabidiol (CBD) exposure alters thermal pain sensitivity, problem-solving, and prefrontal cortex excitability. *Mol. Psychiatry* **2023**, *28*, 3397–3413. [CrossRef]
61. Costa, H.H.V.; Vilela, F.C.; Giusti-Paiva, A. Continuous central infusion of cannabinoid receptor agonist WIN 55,212-2 decreases maternal care in lactating rats: Consequences for fear conditioning in adulthood males. *Behav. Brain Res.* **2013**, *257*, 31–38. [CrossRef]
62. Gray, K.A.; Day, N.L.; Leech, S.; Richardson, G.A. Prenatal marijuana exposure: Effect on child depressive symptoms at ten years of age. *Neurotoxicol. Teratol.* **2005**, *27*, 439–448. [CrossRef]
63. Leech, S.L.; Larkby, C.A.; Day, R.; Day, N.L. Predictors and Correlates of High Levels of Depression and Anxiety Symptoms Among Children at Age 10. *J. Am. Acad. Child. Adolesc. Psychiatry* **2006**, *45*, 223–230. [CrossRef] [PubMed]
64. Peterson, C.S.; Ifionu, I.; Hamood, F.; Semizeh, H.; Ali, A.; Noble, D.; Qiao, M.; Borgland, S.L. Prenatal and early postnatal cannabis exposure interactions with adolescent chronic stress on anxiety-like, depression-like, and risk-taking behaviour. *Psychopharmacology* **2025**. [CrossRef]
65. Traccis, F.; Serra, V.; Sagheddu, C.; Congiu, M.; Saba, P.; Giua, G.; Devoto, P.; Frau, R.; Cheer, J.F.; Melis, M. Prenatal THC Does Not Affect Female Mesolimbic Dopaminergic System in Preadolescent Rats. *Int. J. Mol. Sci.* **2021**, *22*, 1666. [CrossRef] [PubMed]
66. Hall, W.; Degenhardt, L. Cannabis use and the risk of developing a psychotic disorder. *World Psychiatry* **2008**, *7*, 68–71. [CrossRef] [PubMed]
67. Fontes, M.A.; Bolla, K.I.; Cunha, P.J.; Almeida, P.P.; Jungerman, F.; Laranjeira, R.R.; Bressan, R.A.; Lacerda, A.L.T. Cannabis use before age 15 and subsequent executive functioning. *Br. J. Psychiatry* **2011**, *198*, 442–447. [CrossRef]
68. Clarke, J.R.; Rossato, J.I.; Monteiro, S.; Bevilaqua, L.R.M.; Izquierdo, I.; Cammarota, M. Posttraining activation of CB1 cannabinoid receptors in the CA1 region of the dorsal hippocampus impairs object recognition long-term memory. *Neurobiol. Learn. Mem.* **2008**, *90*, 374–381. [CrossRef] [PubMed]
69. Fanselow, M.S. Contextual fear, gestalt memories, and the hippocampus. *Behav. Brain Res.* **2000**, *110*, 73–81. [CrossRef]
70. Pamplona, F.A.; Takahashi, R.N. WIN 55212-2 impairs contextual fear conditioning through the activation of CB1 cannabinoid receptors. *Neurosci. Lett.* **2006**, *397*, 88–92. [CrossRef]
71. Lightfoot, S.H.M.; Nastase, A.S.; Costa Lenz Cesar, G.; Hume, C.; Gom, R.C.; Teskey, G.C.; Hill, M.N. Acute and chronic cannabis vapor exposure produces immediate and delayed impacts on phases of fear learning in a sex specific manner. *Psychopharmacology* **2025**. [CrossRef]
72. Ballinger, M.D.; Saito, A.; Abazyan, B.; Taniguchi, Y.; Huang, C.-H.; Ito, K.; Zhu, X.; Segal, H.; Jaaro-Peled, H.; Sawa, A.; et al. Adolescent cannabis exposure interacts with mutant DISC1 to produce impaired adult emotional memory. *Neurobiol. Dis.* **2015**, *82*, 176–184. [CrossRef]
73. Jacob, W.; Marsch, R.; Marsicano, G.; Lutz, B.; Wotjak, C.T. Cannabinoid CB1 receptor deficiency increases contextual fear memory under highly aversive conditions and long-term potentiation in vivo. *Neurobiol. Learn. Mem.* **2012**, *98*, 47–55. [CrossRef]
74. Duperrouzel, J.; Hawes, S.W.; Lopez-Quintero, C.; Pacheco-Colón, I.; Comer, J.; Gonzalez, R. The Association between Adolescent Cannabis Use and Anxiety: A Parallel Process Analysis. *Addict. Behav.* **2018**, *78*, 107–113. [CrossRef] [PubMed]

75. De Gregorio, D.; Dean Conway, J.; Canul, M.-L.; Posa, L.; Bambico, F.R.; Gobbi, G. Effects of chronic exposure to low doses of Δ9-tetrahydrocannabinol in adolescence and adulthood on serotonin/norepinephrine neurotransmission and emotional behaviors. *Int. J. Neuropsychopharmacol.* **2020**, *23*, 751–761. [CrossRef] [PubMed]
76. Garcia-Mompo, C.; Curto, Y.; Carceller, H.; Gilabert-Juan, J.; Rodriguez-Flores, E.; Guirado, R.; Nacher, J. Δ-9-Tetrahydrocannabinol treatment during adolescence and alterations in the inhibitory networks of the adult prefrontal cortex in mice subjected to perinatal NMDA receptor antagonist injection and to postweaning social isolation. *Transl. Psychiatry* **2020**, *10*, 177. [CrossRef]
77. Godino, M.C.; Torres, M.; Sánchez-Prieto, J. Inhibition of N- and P/Q-type Ca2+ channels by cannabinoid receptors in single cerebrocortical nerve terminals. *FEBS Lett.* **2005**, *579*, 768–772. [CrossRef] [PubMed]
78. Twitchell, W.; Brown, S.; Mackie, K. Cannabinoids Inhibit N- and P/Q-Type Calcium Channels in Cultured Rat Hippocampal Neurons. *J. Neurophysiol.* **1997**, *78*, 43–50. [CrossRef] [PubMed]
79. Huizink, A.C.; Mulder, E.J.H. Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. *Neurosci. Biobehav. Rev.* **2006**, *30*, 24–41. [CrossRef]
80. Sorkhou, M.; Singla, D.R.; Castle, D.J.; George, T.P. Birth, cognitive and behavioral effects of intrauterine cannabis exposure in infants and children: A systematic review and meta-analysis. *Addiction* **2024**, *119*, 411–437. [CrossRef]
81. Keles, H.O.; Radoman, M.; Pachas, G.N.; Evins, A.E.; Gilman, J.M. Using Functional Near-Infrared Spectroscopy to Measure Effects of Delta 9-Tetrahydrocannabinol on Prefrontal Activity and Working Memory in Cannabis Users. *Front. Hum. Neurosci.* **2017**, *11*, 488. [CrossRef]
82. Spear, L.P. Adolescent neurobehavioral characteristics, alcohol sensitivities, and intake: Setting the stage for alcohol use disorders? *Child. Dev. Perspect.* **2011**, *5*, 231–238. [CrossRef]
83. Jacobus, J.; Tapert, S.F. Effects of Cannabis on the Adolescent Brain. *Curr. Pharm. Des.* **2014**, *20*, 2186–2193. [CrossRef]
84. Scott, J.C.; Slomiak, S.T.; Jones, J.D.; Rosen, A.F.G.; Moore, T.M.; Gur, R.C. Association of Cannabis with Cognitive Functioning in Adolescents and Young Adults: A Systematic Review and Meta-analysis. *JAMA Psychiatry* **2018**, *75*, 585–595. [CrossRef] [PubMed]
85. Holliday, E.; Bagasra, A. Challenges in Recovery Research from a Neuroscience Perspective. *Addict. Addict. Disord.* **2023**, *10*, 120. [CrossRef]