Developmental Impact

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Introduction

The endocannabinoid system (ECS) is the primary endogenous system through which exogenous cannabinoids act. Please see Chap. 1 for a review of the outlines the components of the endocannabinoid system. The ECS is a highly evolutionarily conserved system, which suggests the developmental processes modulated by the ECS are vital for normal development. As reviewed by Harkany et al., the ECS is present from the earliest stages of pregnancy and regulates key aspects of fertilization and implantation [1]. Anandamide (AEA), a primary endocannabinoid, facilitates fertilization through cannabis 1 receptors (CB1R) expressed on spermatozoa. Subsequently, transient reductions in AEA in the uterus and CB1R and CB2R expression in the embryo facilitate blastocyst activation and enable implantation into the uterine wall.

Neurodevelopment

As the fetus continues to develop, the ECS also plays a fundamental role in regulating multiple stages of brain development (neurodevelopment) and modulates the mature nervous system throughout adulthood (Highlights Box 4.1) [1–3]. Neurodevelopment begins early in embryogenesis and continues through young adulthood, presenting a uniquely vulnerable time to the detrimental effects of cannabis use (Fig. 4.1). Throughout neurodevelopment, CB1R is widely expressed and is one of the most abundant G-protein-coupled receptors in the brain [1, 3]. CB1R is detectable in the human fetal brain at approximately 14 weeks gestation. Expression progressively increases in a temporally and spatially regulated pattern in the cerebral cortex, caudate nucleus, putamen, cerebellar cortex, hippocampus,

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Highlights Box 4.1 Key Points in Neurodevelopment

- The ECS is an important regulator of fetal development from conception.
- The ECS regulates many aspects of brain development, including organization of the brain into mature neural circuits, which continues until about 25 years old.
- The ECS also mediates development of neurotransmitters important to cognitive function and mental health, including glutamate, serotonin, dopamine, and opioid systems.
- Behavioral functions regulated ECS signaling include cognition, learning and memory, attention, drug/addictive behaviors, social interactions, pain sensitivity, sexual behavior, and stress response.
- Over the lifespan, the ECS continues to mediate behavioral functions and the ability of the brain to learn and adapt, forming new memories and refining learned functions.

and amygdala. Further, endocannabinoids are "made on demand," facilitating maintenance of a precise temporal and spatial pattern of signaling [1, 3]. 2-arachidonoylglycerol (2-AG) concentrations are 1000-fold higher throughout brain development, setting a basal tone for the ECS. Conversely, AEA levels are relatively low at midgestation and gradually increase throughout the perinatal period and into adolescence.

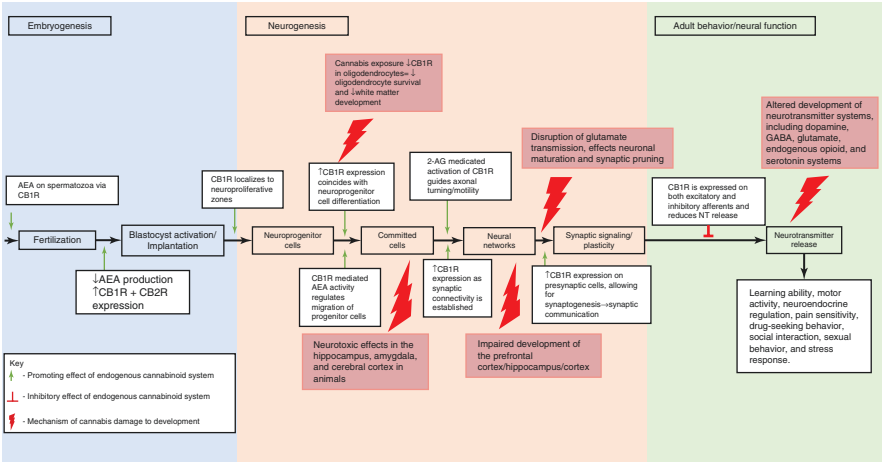

Fig. 4.1 The effects of prenatal cannabis exposure throughout neurodevelopment. Stages of development during embryogenesis, ongoing neurogenesis, and adult neural function are presented. The stages of neurogenesis are presented sequentially for simplicity. It is important to note these stages take place simultaneously and at different times and rates throughout the developing brain. White boxes show the role of and changes in the endocannabinoid system across development. Key points of exogenous cannabis exposure are presented in the red boxes

Neuromaturation: Neurogenesis, Synaptogenesis, and Myelination

Development of the brain begins with a collection of neuronal progenitor cells, which must migrate to specific locations in the brain, differentiate to specific types of neurons (neuronal differentiation), and form a network of connections or synapses. Synaptic pruning then refines connections to establish neuronal circuits. The ECS regulates many aspects of neuronal differentiation, including neurogenesis, neuronal migration, neurite outgrowth, and axonal pathfinding (Fig. 4.1) [1, 4]. Temporal and spatial expression of endocannabinoids and receptors is also important in maintaining homeostatic control of synaptic transmission in the developmental brain in a narrow physiological time window [5].

Endocannabinoid signaling, particularly AEA-mediated signaling, regulates survival of and differentiation of neuronal progenitor cells, ensuring adequate quantities of cells during neurodevelopment [1]. CB1R localizes to cell proliferative regions including the subventricular zones of the striatum, nucleus accumbens, and neocortex [6, 7]. There is a robust upregulation of CB1R expression that coincides with commitment of neuronal progenitor cells to differentiate, and endocannabinoid signaling subsequently mediates acquisition of neuronal identity and initial organization of neural networks [6]. As development continues the distribution of CB1R shifts to the cerebral cortex, coinciding with neuronal cell migration through the cortex to their final target site [2]. Through CB1R signaling, AEA is proposed to regulate migration of progenitor cells and neurons into the cortical plate, as well as long-distance migration of interneurons [4].

As neurons reach their target sites and development progresses, CB1R expression increases on axons and axonal growth cones along developing axonal trajectories, or white matter [1]. CB1R levels subsequently peak when synaptic connectivity is established [7]. CB1 receptors cluster at anchor points in immature neuronal networks to facilitate information processing. As neurons reach their destination, axonal growth cones orchestrate axon tract development. 2-AG-mediated activation of CB1R in axonal growth cones helps guide directional turning and impacts motility of the developing axon [8].

These CB1R expression sites along axons are termed “atypical” because this is a unique distribution pattern that only exists in the developing brain and is essentially absent from the fully developed brain [2]. Considering these unique developmental expression patterns, endocannabinoid-mediated signaling is widely implicated in the organization of long-range axon tract development including corticothalamic and corticospinal tracts [3, 4]. The role of the ECS in axonal guidance is supported by animal studies, which demonstrate deletion or blockade of CB1R results in increased aberrant axon trajectories in the corpus callosum and abnormal fasciculations of long-range axons [3, 4]. As axonal fasciculations and pathways develop, 2-AG mediates activation of radial glial cells and oligodendrocytes to regulate myelination, further establishing mature neural circuits [4].

As neural circuits form, CB1R expression is enriched on presynaptic neurons [1, 3]. Endocannabinoid-mediated retrograde signaling at central synapses allows

control of the earliest events of presynaptic neurotransmitter release during the transition from synaptogenesis to synaptic communication in developing neuronal circuits [6]. This pattern of expression continues in the adult brain, enabling ECS-mediated regulation of synaptic transmission and of adult synaptic plasticity [6].

Neurotransmitter System Development

As with neuronal circuit formation, the ECS also mediates development of multiple neurotransmitter systems (Box 4.1). CB1R is expressed on glutamatergic, cholinergic, glycinergic, and serotonergic neurons [4]. ECS signaling also targets other neurotransmitters, including dopamine, orexin A, adenosine 2A, and delta and mu opioid receptors. Interestingly, dopaminergic, or tyrosine hydroxylase (TH)-containing, neurons express CB1R only during neurodevelopment [2]. CB1R is expressed on both excitatory and inhibitory afferents, and endocannabinoid-mediated signaling generally decreases neurotransmitter release [6]. Through these neurotransmitter systems, the ECS mediates several behavioral functions, including learning ability, motor activity, neuroendocrine regulation, and pain sensitivity, as well as drug-seeking behavior, social interaction, sexual behavior, and stress response.

Neurodevelopmental Impact of Cannabinoid Exposure

Determining the neurodevelopmental impact of cannabinoid exposure is complicated by cannabinoid pharmacodynamics, developmental timing of exposure, overall dose and duration of exposure, and gender, among other factors.

Cannabinoid Potency and Timing of Exposure

Whereas endocannabinoid signaling lasts seconds, exposure to exogenous cannabinoids, such as smoking or ingestion of cannabis, results in more sustained (minutes to hours) and much more indiscriminate signaling patterns [4]. Further, the potency of cannabinoids varies dramatically between cannabis products. Tetrahydrocannabinol (THC), the primary psychoactive cannabinoid, is a potent, low-efficacy cannabinoid receptor agonist that outcompetes endocannabinoids for receptor binding [6]. On the other hand, cannabidiol (CBD), a primary cannabinoid of pharmaceutical or medical interest, is a negative allosteric modulator of CB1R and attenuates activation by THC and endocannabinoids. Like THC, synthetic cannabinoids exhibit high potency and high efficacy. The physiologic and neurodevelopmental impacts of varying formulations of cannabinoid concentrations and ratios are not well understood.

Animal models allow more controlled experimental settings, where researchers determine the timing, formulation, dose, and duration of exposure, when

compared to human consumption of cannabis. These animal studies provided initial insights that neurodevelopment is a unique period of vulnerability to the detrimental effects of cannabinoids on the brain [9]. As reviewed by Lubman and Schneider, exposure to exogenous cannabinoids during neurodevelopment results in impairments of neuronal differentiation and survival, alterations in neurotransmitter system development, cognitive impairments, hyperactivity, cross-tolerance with other illicit drugs and alterations to the opioid system, and learning and memory deficits (Highlights Box 4.2) [9, 10]. Animals exposed to cannabinoids during neurodevelopment, comparable to childhood through young adulthood, show continued neurocognitive impairments, even after periods of abstinence. However, animals who are exposed to cannabinoids after completion of neurodevelopment, comparable to adulthood after approximately 25 years old, do not exhibit similar vulnerabilities.

Highlights Box 4.2 Cognitive Effects of Cannabis Exposure

- Endocannabinoids are made "on demand" to maintain tight temporal and spatial signaling lasting seconds.
- Exogenous cannabinoid exposure results in sustained, indiscriminate signaling.
- Cannabis exposure during neurodevelopment impairs neural circuit formation and neuron survival and alters development of neurotransmitter systems.
- Affected behavioral functions include cognition, learning and memory, emotional reactivity, drug-seeking/addictive behavior, and depression and anxiety.

Prenatal exposure

- Teratogenicity: fetal growth restriction and lower birth weight for gestational age.
- Infancy: increased startle response and irritability, altered sleep patterns.
- Childhood: short-term memory and verbal reasoning impairment, deficits in sustained attention, and increased hyperactivity and impulsivity, as well as higher rates of depression.
- Adolescents: changes in attentional behavior and adaptive learning and higher rates of depression and problematic substance use.

Adolescent exposure

- Brain development continues through young adulthood (about age 25 years old).
- Imaging studies show changes in brain structure and connectivity.
- Impacts psychomotor speed (athletics and driving), complex attention, learning and memory, abstract reasoning, decision making, processing speed, attention, and working memory.

- Associated with higher rates of depression, anxiety, and psychosis.
- Cannabis use at least 4 days per week is associated with decrease in full-scale IQ of approximately 8 points, lower grade point average, and poorer scholastic aptitude test scores.
- Cannabis use of 10 days a month is associated with increased risky and impulsive decision making.
- Earlier age of onset, duration of use, and frequency of use increase risk of negative cognitive impacts.
- Impairments in executive functioning persist even in abstinence.

Mechanisms of Exogenous Cannabinoid Exposure

The increased vulnerability to the detrimental effects of cannabinoids during fetal development is likely due to the vital roles of the ECS in modulating neurodevelopment. One mechanism of exogenous cannabinoid exposure is downregulation of CB1R, which is observed to a much higher degree in the developing brain [11]. Prolonged cannabis exposure downregulates CB1R in oligodendrocytes, which may impact oligodendrocyte survival, resulting in decreased myelination and altered white matter development. Additionally, prenatal cannabinoid exposure disrupts glutamate transmission, which regulates neuronal maturation and synaptic pruning [9]. Cannabinoid exposure also alters expression of genes that regulate neuron proliferation, migration, and synaptogenesis [12].

Exogenous cannabinoid exposure also impacts the development of neurotransmitter systems, including dopamine, GABA, glutamate, endogenous opioid, and serotonin systems [2, 4]. To better understand how cannabis exposure during pregnancy impacts the development of neurotransmitter systems, the Hurd lab characterized midgestational fetal brains [7, 13]. Maternal cannabis use is associated with a reduction of dopamine D2 receptor density in the amygdala in a dose-dependent manner, such that moderate to high cannabis use ($\geq$0.4 joints/day) is associated with the lowest levels of D2 receptor expression [7]. The frontostriatopallidal proenkephalin/D2 receptor circuit maps onto inhibitory control behavior, and downregulation predicts more impulsive behavior in cannabis-exposed offspring. Changes in enkephalin/D2 receptor density in the amygdala and nucleus accumbens, which mediate emotion and reward, are also implicated in depression, drug addiction, and schizophrenia [14]. Reward and addictive behaviors are also modulated by interactions between the ECS and opioid system [7]. Particularly proenkephalin containing neurons, which target mu and delta opioid receptors, are sensitive to prenatal THC exposure. Animal studies also support this predisposition for substance use, with offspring exposed to cannabis in utero demonstrating increased impulsivity and self-administration of heroin and cocaine, which is associated with alterations in metabolic activity in the frontal lobe and amygdala [7].

Teratogenicity of Exogenous Cannabinoids

In addition to the central nervous system, the ECS is expressed as a regulatory signaling system in multiple developing organ systems [1]. To date, the teratogenicity of exogenous cannabinoid exposure is not well understood. In animal models, early prenatal exposure before or during organogenesis or exposure to high cannabinoid doses (up to 60 mg/kg over a period of 1–3 months) resulted in neurotoxic effects in the hippocampus, amygdala, and cerebral cortex [9], with some animal models showing neurotoxicity comparable to fetal alcohol syndrome [2]. Of note, these studies investigated exposures much higher than typical human consumption.

While animal models raised concerns for teratogenic effects of exogenous cannabinoids, there has been little evidence to support gross developmental abnormalities in humans. The Generation R Study, a prospective study of 7452 mothers to investigate the impact of substance use during pregnancy on fetal growth, found maternal cannabis in early pregnancy (<18 weeks gestation) or continued use throughout pregnancy is associated with growth restriction in mid to late pregnancy and lower birth weight [15]. El Marrouin et al. also demonstrated a dose response, with no significant changes in birth weight among the children of occasional (monthly) cannabis-using women, significantly lower birth weight among children of moderate (weekly) cannabis-using women, and the lowest birth weights among heavy (daily) cannabis-using women. To further investigate the impact of maternal cannabis use on fetal growth and development, Hurd et al. characterized midgestational postmortem human fetuses [13]. Exposed fetuses had a significant reduction in foot length and body weight for gestational age, with fetal foot length negatively correlating with the amount and frequency of maternal cannabis use.

Cognitive Effects of Prenatal Cannabis Exposure

CB1R is highly expressed in striatal, limbic, and cortical regions that coordinate cognitive and emotional function [11]. Similarly, there is a high density of CB1R in the hippocampus, which is fundamental to memory acquisition, consolidation, and retrieval [9]. Specific brain regions impacted by prenatal cannabis exposure provide insights into the expected neurocognitive impacts (Box 4.2). For example, development of the prefrontal cortex appears particularly vulnerable to maternal cannabis use, resulting in disinhibition that may underly many of the cognitive deficits associated with long-term cannabis use. Reductions in cortical neuronal cell populations and decreased glutamatergic neurotransmission in newborn rats have also been observed in prenatal cannabis exposure, which may contribute to learning deficits and decreased emotional reactivity [16]. In the hippocampus, prenatal THC exposure disrupts neuronal migration, elongation of GABA-containing interneurons, and synaptogenesis, predicting impairments in memory and learning [1, 7]. Disruption of endocannabinoid signaling in the hippocampus and cortex (particularly the frontal lobe) predicts cognitive, memory, and neurobehavioral deficits [17].

Neurodevelopmental vulnerability to exogenous cannabinoid exposure is of particular concern during the perinatal period. Cannabinoids are lipophilic, readily cross the blood-brain barrier, and reach the brain of fetuses and newborns [2]. Approximately one-third of plasma THC undergoes cross-placental transfer during pregnancy [1, 4]. In utero cannabinoid exposure is associated with reorganization of neurotransmitter systems and cortical cell death and concurrent impairments in executive function, learning and memory, attention, visual perceptive tasks, and language comprehension and increased impulsivity and externalizing behavior [9, 17].

Multiple confounders, including comorbid tobacco and alcohol use, sociodemographic factors, and other psychological characteristics, have complicated studies of the neurodevelopmental consequences of maternal cannabis use during pregnancy. Most of the information on the developmental outcomes of prenatal cannabis exposure is derived from the Ottawa Prenatal Prospective Study (OPPS) and the Maternal Health Practices and Child Development Study (MHPCD), which followed the children of women who used cannabis, tobacco, and or alcohol from birth through adolescence [4]. The OPPS primarily enrolled low-risk Caucasian, middle class Canadian women to study prenatal exposure to tobacco and cannabis, whereas the MHPCD followed women generally of low socioeconomic status from Pittsburgh, approximately half of whom are Caucasian and half of whom are Black. The following sections will review key findings from the OPPS and MHPCD studies of the postnatal impact of maternal cannabis use during pregnancy through infancy, childhood, and adolescence (Fig. 4.2).

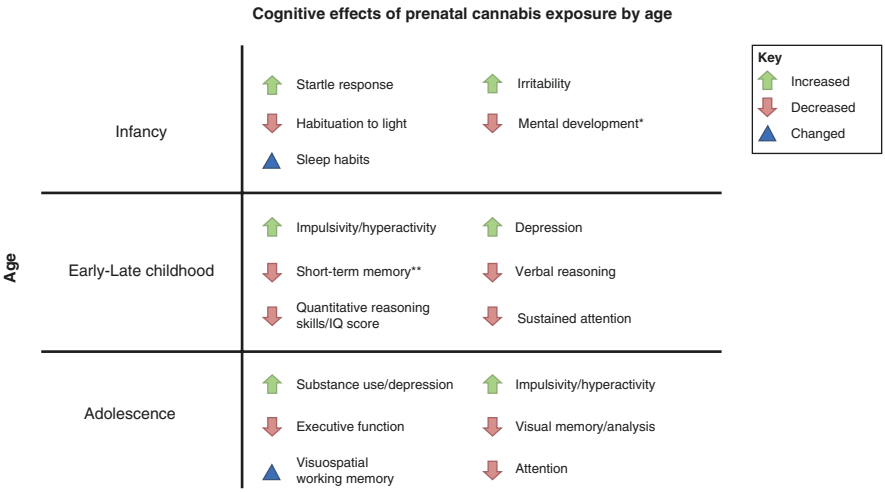

Fig. 4.2 The impact of prenatal cannabis exposure on neurocognition. This figure presents neurocognitive changes associated with prenatal cannabis exposure as reported in the MHPCD and OPPS longitudinal studies of maternal cannabis use. Findings are presented by age group: Infancy (birth to 3 years old), Early-Late childhood (3–13 years old), and Adolescence (14–22 years old). * Development changes were not present at 18 months of age in the MHPCD cohort and the OPPS did not report cognitive deficits between the ages of 1 and 3 years. ** Analysis by race between White and Black mothers shows disparities in effects of maternal cannabis use

Infancy

In neonates, prenatal cannabis exposure was strongly associated with increased startle response and a significant reduction in habituation to light, as well as altered sleep patterns and a trend toward increased irritability [4]. In the MHPCD cohort, using more than one joint per day in the third trimester was associated with decreased mental scores on the Bayley Scales of Infant Development at 9 months of age, which disappeared by 18 months old [4]. Similarly, the OPPS did not report cognitive deficits between the ages of 1 and 3 years, suggesting cognitive abnormalities are absent or subclinical in toddlers. In a third longitudinal study of prenatal cannabis exposure, Richardson et al. found use of one or more joints per day during the third trimester was associated with delayed mental development at 9 months of age [18].

Early Through Late Childhood

By age 3 years, first- or second-trimester cannabis exposure was associated with short-term memory (-1.1 IQ points/joint/day and -2.3 IQ points/joint/day, respectively) in the MHPCD cohort [19]. When analyzing the impact of prenatal cannabis use by race, a more complex interaction emerges. Among the children of Black mothers, there was a significant impact of first-trimester cannabis use on composite score (-0.9 IQ points/joint/day), short-term memory subscale (-1.1 IQ points/joint/day), and verbal reasoning (-1.5 IQ points/joint/day). Second-trimester use was also significantly associated with lower short-term memory subscores (-1.8 IQ points/joint/day). Interestingly, among the children of White mothers, there was no significant effect of prenatal cannabis use during any trimester of pregnancy on the composite IQ or subscale scores, which may be mediated or offset by participation in daycare or preschool. Similar to the main findings of the MHPCD study, in the OPPS study, smoking six or more joints a week (heavy exposure) during pregnancy was associated with decreases in verbal perceptual, general cognitive index, and memory domain scores of the McCarthy Scales of Children's Abilities at 4 years of age [20]. Thus, both studies support the impact of prenatal cannabis exposure cognitive functions including short-term memory and verbal reasoning in early childhood, though it is important to note other factors may mediate or confound the impact of exposure.

At age 5 years, in the OPPS cohort, prenatal cannabis exposure was associated with a dose-dependent trend in deficits of sustained attention, with the highest omission error rate in children of mothers who used more than six joints a week and the lowest omission error rate in children whose mothers used no more than one joint a week [21]. While heavy use mothers reported higher ratings on an impulsive/hyperactive scale, these differences were not statistically significant. In the MHPCD cohort, at age 6 years, heavy cannabis use (one or more joints a day) during the first or second trimester is associated with lower verbal reasoning scores [22]. Heavy cannabis use during the second trimester is also associated with deficits in

short-term memory and during the second or third trimester is associated with decreased quantitative scores. In any trimester, heavy cannabis use is associated with lower composite score and quantitative reasoning. At age 10 years, heavy first- and third-trimester exposure (>0.89 joints/day) is associated with increased hyperactivity and impulsivity, and heavy second-trimester exposure is associated with increased impulsivity [23]. Heavy exposure is also associated with increased levels of depression and lower child IQ.

Adolescence

Synthesis of the findings from OPPS and MHPCD through adolescence shows prenatal cannabis exposure adversely impacts adolescent executive function, particularly attentional behavior and visual analysis and hypothesis testing, with impacts lasting through childhood [4]. By age 13–16 years, adolescents in the OPPS cohort with heavy cannabis exposure (>0.86 joints/day) exhibited deficits in visual memory, visual analysis, and ability to maintain attention [4]. Similarly, adolescents in the MHPCD cohort demonstrate deficits in visual analysis and impulse control aspects of executive functioning. A functional magnetic resonance imaging (fMRI) study of 18–22-year-old youth showed prenatal exposure is associated with alternations in neural activity during visuospatial working memory tasks [4]. Maternal cannabis use predicts earlier onset and increased frequency of substance use among adolescent children [7].

Cognitive Effects of Adolescent Cannabis Exposure

Similar to prenatal exposure, cannabis use by adolescents and young adults prior to completion of neurodevelopment poses an increased risk to the cognitive effects of cannabis use. The ECS continues to function as a modulator of neurodevelopment via regulation of synaptic pruning and signaling pathways, which facilitate learning, memory, appetite, and neuroprotection and modulate anxiety, depression, and pain [4]. Cannabis use impacts psychomotor speed, complex attention, planning and sequencing ability, executive function, and working memory [7]. Epidemiologic studies report adolescents with heavy cannabis use experience higher rates of depression and anxiety, a greater burden of psychotic symptoms, impairments in learning and memory, and deficits in executive functioning, including decision-making, processing speed, and attention [9]. Similarly, a review of studies of cognition demonstrates diminished performance on tasks requiring effortful performance, including executive functioning, verbal free recall, decision-making, abstract reasoning, and complex spatial work [24, 25].

While the literature investigating the cognitive effects of adolescent cannabis use is expanding, synthesis of evidence is limited by variable outcome measures, relatively small study sizes, and inconsistency in reporting the frequency or quantity of cannabis use between studies. Where available, frequency or quantity of cannabis

use associated with reported neurologic changes or impairments will be noted. One of the most provocative findings was reported by Meier et al., who followed 1037 individuals from birth, with neuropsychological testing at 13 years and 38 years of age [26]. In this cohort, persistent cannabis use (at least 4 days per week) is associated with a greater decline in neuropsychological function assessed by full-scale IQ (WAIS-IV) of approximately eight points, as well as declines in verbal IQ, performance IQ, and multiple other subtests. Impairments were noted in executive function, memory, processing speed, perceptual reasoning, verbal comprehension, and verbal learning and recall. Of note, adolescent-onset cannabis users did not fully regain neuropsychological functioning with abstinence, supporting the neurotoxic effects of cannabis on the developing brain.

Subsequently, there has been a robust debate about the impact of cannabis use on IQ and interest in how this correlates with academic performance. Persistent cannabis use throughout high school is associated with lower grade point average (GPA) and scholastic aptitude test scores, though these observations were not significant after controlling for alcohol and tobacco use [25, 27]. One contributor of poorer academic performance may be externalizing and attention/concentration problems, which often co-occur with cannabis use [25].

To better understand the impact of cannabis use on neurodevelopment and cognition, Becker et al. conducted a prospective analysis of cannabis-using adolescents who used at least five times per week for at least 1 year, with onset of use before age 17 years [24]. Individuals were selected who were sober at the time of enrolment, effectively limiting the evaluation to the effects of chronic cannabis use. In these adolescents, there was decreased white matter growth in the central and parietal regions of the right and left superior longitudinal fasciculus, which is associated with diminished performance in verbal learning and memory [24, 25]. As described in the study, more "hits" or uses of cannabis are negatively associated with changes in white matter connectivity in a seemingly dose-dependent manner.

Similarly, in a second longitudinal study, Camchong et al. followed treatment-seeking adolescents with more than 50 lifetime "exposures to" (or uses of) cannabis who were sober at the time of study entry (29). In this cohort, decreased functional connectivity between caudal anterior cingulate cortex and superior frontal gyrus predicted higher amounts of cannabis use in the following months defined as number of days used. More frequent cannabis use also predicted lower intelligence quotient (IQ), though this was a nonsignificant trend when including alcohol as covariate, and slower cognitive function [25, 28]. The study authors propose one possible mechanism may be increased dopamine release in the anterior cingulate cortex, resulting in reciprocal downregulation of D2 receptor availability and subsequent impairment of cognitive functioning and decision-making.

The frequency of and the age of onset of cannabis use are also associated with a negative impact on working memory including recall time and sustained attention. In the Philadelphia Neurodevelopmental Cohort, adolescents who reported frequent cannabis use (more than three times per week) performed worse on measures of executive control compared to occasional cannabis users (twice per week or less) and non-using adolescents [29]. Earlier age of onset is associated with worse

performance in occasional users, though this group exhibited better executive control, memory, and social cognition. In a study by Solowij et al., cannabis users (average 14 days of use per month) exhibited impaired verbal learning and memory over five study procedure trials, with impairment in learning, retention, and retrieval [30]. Younger age of onset, longer duration, and more frequent or higher quantity of cannabis use are all associated with fewer total words learned and recalled. Additionally, adolescents who use cannabis an average of 10 days per month show increased risky and impulsive decision makers, adopting strategies with higher levels of uncertainty and utilizing information less efficiently [31].

Similar to animal models, impairments in executive function associated with adolescent cannabis use are more persistent in abstinence when compared with adult cannabis users [9]. Earlier age of onset is associated with greater impairment in learning and memory, decision-making, attention, and other executive functions. Among adult users, those who began using prior to age 16 years show deficits in visual scanning, sustained attention, and working memory compared to late-onset and non-using adults [11]. In a study of adults who chronically use cannabis, onset in adolescence before age 15 years (mean use of 1.7 joints per day) is associated with poorer cognitive performance in executive functioning in adulthood [32]. Similarly, a second study demonstrated onset of use prior to age 16 years (average 24.8 smoking episodes and 14.8 g cannabis consumed per week) is associated with poorer cognitive performance on measures of executive function, with more difficulty inhibiting inappropriate responses and maintaining cognitive set [33]. In these individuals, earlier age of onset is positively correlated with changes in frontal white matter tracts as assessed by fractional anisotropy [34]. Taken together these findings suggest that impairments in executive function and cognition may result from adolescent cannabis use and persist into adulthood due to alterations in neurodevelopment.

Neuroimaging Studies of Adolescent Cannabis Use

Neuroimaging studies have identified mixed results regarding structural changes associated with adolescent cannabis use. For detailed reviews of neuroimaging findings please see Chye et al. [11]. Synthesis of neuroimaging studies is limited by small study size, heterogeneity of population and techniques, and multiple other confounders. Yet, two regions in which structural changes are often noted in cross-sectional and longitudinal structural and functional studies are the frontal lobe, particularly orbitofrontal cortex (OFC), and parietal lobes. Reduced frontal lobe thickness is also predictive of adolescent-onset cannabis use in adult users. As with cognitive impairments, earlier age of onset may be associated with the magnitude of structural change. However, changes in brain structure are not necessarily equivocal to functional changes. For example, another more consistent finding is smaller bilateral hippocampi in adolescents who use cannabis compared with non-using peers. One study found hippocampal volume is positively associated with verbal learning performance in adolescents who do not use cannabis, whereas it is not associated

with verbal learning in cannabis-using adolescents, suggesting altered structure-functional relationship may underlie cognitive differences associated with adolescent cannabis use.

As imaging technologies have advanced, there has been more focus on evaluating white matter integrity and structure-functional relationships. Longitudinal studies suggest continued heavy cannabis use alters development of white matter microstructure and may contribute to functional impairments [24]. The most consistently implicated findings are poorer white matter integrity in the superior longitudinal fasciculus, the superior temporal gyrus, and the corpus callosum [11, 24]. Poorer white matter integrity has been reported in axon fibers encompassing the frontal lobe and bilateral hippocampi. Frontal and bilateral parietal lobe activation is also implicated in attention network task-based connectivity, with adolescent cannabis users showing greater activation and poorer task performance. This suggests adolescents who use cannabis may compensate with increased brain activation to mitigate functional impairment.

One notable limitation of neuroimaging studies is that the directionality of change is not known. In other words, it is not known if differences in neuroimaging result in behaviors that are associated with more frequent cannabis use or if cannabis use alters brain structure and connectivity. The Adolescent Brain Cognitive Development (ABCD) study (https://abcdstudy.org) is a multisite prospective longitudinal study now underway that may help to better understand the contribution of cannabis and other substance use, age of onset, and gender, among other biological and behavioral determinants, on neurodevelopmental trajectory.

Future Directions

Taken together, what is known about the role of the ECS in neurodevelopment and the impact of cannabinoid exposure during the prenatal and adolescent periods, findings suggest adolescence is a critical period of increased risk for adverse outcomes from cannabis use [9]. No amount of cannabis is known to be safe for the developing brain. However, much remains unknown. Very little is known about the impact of prenatal cannabinoid exposure and adolescent cannabis use on the ECS. Further, to date no studies have evaluated the effects of prenatal or adolescent cannabinoid exposure on endocannabinoid levels. Animal studies and clinical experience also suggest there may be notable differences between genders that are not well understood [10, 11]. Many of the studies completed to date are cross-sectional or retrospective and do not allow for adequate evaluation of confounders or causality [9]. Similarly, longitudinal studies have yet to be conducted to investigate the unprecedented increases in THC concentration and routes of administration as recreational cannabis is increasingly legalized and commercialized. The past decade of legalization has been predominantly driven by political processes. Medicine and science must now respond with evidence-based studies to better understand the impact these changes are having on youths' developing brains.

References

1. Harkany T, Guzman M, Galve-Roperh I, Berghuis P, Devi LA, Mackie K. The emerging functions of endocannabinoid signaling during CNS development. Trends Pharmacol Sci. 2007;28(2):83–92.
2. Fernandez-Ruiz J, Berrendero F, Hernandez ML, Ramos JA. The endogenous cannabinoid system and brain development. Trends Neurosci. 2000;23(1):14–20.
3. Lu HC, Mackie K. Review of the endocannabinoid system. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021;6(6):607–15.
4. Wu CS, Jew CP, Lu HC. Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. Future Neurol. 2011;6(4):459–80.
5. Bernard C, Milh M, Morozov YM, Ben-Ari Y, Freund TF, Gozlan H. Altering cannabinoid signaling during development disrupts neuronal activity. Proc Natl Acad Sci U S A. 2005;102(26):9388–93.
6. Harkany T, Mackie K, Doherty P. Wiring and firing neuronal networks: endocannabinoids take center stage. Curr Opin Neurobiol. 2008;18(3):338–45.
7. Jutras-Aswad D, DiNieri JA, Harkany T, Hurd YL. Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcome. Eur Arch Psychiatry Clin Neurosci. 2009;259(7):395–412.
8. Keimpema E, Barabas K, Morozov YM, Tortoriello G, Torii M, Cameron G, et al. Differential subcellular recruitment of monoacylglycerol lipase generates spatial specificity of 2-arachidonoyl glycerol signaling during axonal pathfinding. J Neurosci. 2010;30(42):13992–4007.
9. Lubman DI, Cheetham A, Yucel M. Cannabis and adolescent brain development. Pharmacol Ther. 2015;148:1–16.
10. Schneider M. Cannabis use in pregnancy and early life and its consequences: animal models. Eur Arch Psychiatry Clin Neurosci. 2009;259(7):383–93.
11. Chye Y, Christensen E, Yucel M. Cannabis use in adolescence: a review of neuroimaging findings. J Dual Diagn. 2020;16(1):83–105.
12. Gomez M, Hernandez M, Johansson B, de Miguel R, Ramos JA, Fernandez-Ruiz J. Prenatal cannabinoid and gene expression for neural adhesion molecule L1 in the fetal rat brain. Brain Res Dev Brain Res. 2003;147(1–2):201–7.
13. Hurd YL, Wang X, Anderson V, Beck O, Minkoff H, Dow-Edwards D. Marijuana impairs growth in mid-gestation fetuses. Neurotoxicol Teratol. 2005;27(2):221–9.
14. Wang X, Dow-Edwards D, Anderson V, Minkoff H, Hurd YL. Discrete opioid gene expression impairment in the human fetal brain associated with maternal marijuana use. Pharmacogenomics J. 2006;6(4):255–64.
15. El Marroun H, Tiemeier H, Steegers EA, Jaddoe VW, Hofman A, Verhulst FC, et al. Intrauterine cannabis exposure affects fetal growth trajectories: the generation R study. J Am Acad Child Adolesc Psychiatry. 2009;48(12):1173–81.
16. Antonelli T, Tomasini MC, Tattoli M, Cassano T, Tanganelli S, Finetti S, et al. Prenatal exposure to the CB1 receptor agonist WIN 55,212-2 causes learning disruption associated with impaired cortical NMDA receptor function and emotional reactivity changes in rat offspring. Cereb Cortex. 2005;15(12):2013–20.
17. Wang X, Dow-Edwards D, Keller E, Hurd YL. Preferential limbic expression of the cannabinoid receptor mRNA in the human fetal brain. Neuroscience. 2003;118(3):681–94.
18. Richardson GA, Day NL, Goldschmidt L. Prenatal alcohol, marijuana, and tobacco use: infant mental and motor development. Neurotoxicol Teratol. 1995;17(4):479–87.
19. Day NL, Richardson GA, Goldschmidt L, Robles N, Taylor PM, Stoffer DS, et al. Effect of prenatal marijuana exposure on the cognitive development of offspring at age three. Neurotoxicol Teratol. 1994;16(2):169–75.
20. Fried PA, Watkinson B. 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. J Dev Behav Pediatr. 1990;11(2):49–58.

21. Fried PA, Watkinson B, Gray R. A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marihuana, cigarettes, and alcohol. Neurotoxicol Teratol. 1992;14(5):299–311.
22. Goldschmidt L, Richardson GA, Willford J, Day NL. Prenatal marijuana exposure and intelligence test performance at age 6. J Am Acad Child Adolesc Psychiatry. 2008;47(3):254–63.
23. Day NL, Leech SL, Goldschmidt L. The effects of prenatal marijuana exposure on delinquent behaviors are mediated by measures of neurocognitive functioning. Neurotoxicol Teratol. 2011;33(1):129–36.
24. Becker MP, Collins PF, Lim KO, Muetzel RL, Luciana M. Longitudinal changes in white matter microstructure after heavy cannabis use. Dev Cogn Neurosci. 2015;16:23–35.
25. Cyrus E, Coudray MS, Kiplagat S, Mariano Y, Noel I, Galea JT, et al. A review investigating the relationship between cannabis use and adolescent cognitive functioning. Curr Opin Psychol. 2020;38:38–48.
26. 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 U S A. 2012;109(40):E2657–64.
27. Meier MH, Hill ML, Small PJ, Luthar SS. Associations of adolescent cannabis use with academic performance and mental health: A longitudinal study of upper middle class youth. Drug Alcohol Depend. 2015;156:207–12.
28. Camchong J, Lim KO, Kumra S. Adverse Effects of Cannabis on Adolescent Brain Development: A Longitudinal Study. Cereb Cortex. 2017;27(3):1922–30.
29. Scott JC, Wolf DH, Calkins ME, Bach EC, Weidner J, Ruparel K, et al. Cognitive functioning of adolescent and young adult cannabis users in the Philadelphia Neurodevelopmental Cohort. Psychol Addict Behav. 2017;31(4):423–34.
30. Solowij N, Jones KA, Rozman ME, Davis SM, Ciarrochi J, Heaven PCL, et al. Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. Psychopharmacology. 2011;216(1):131–44.
31. Solowij N, Jones KA, Rozman ME, Davis SM, Ciarrochi J, Heaven PC, et al. Reflection impulsivity in adolescent cannabis users: a comparison with alcohol-using and non-substance-using adolescents. Psychopharmacology (Berl). 2012;219(2):575–86.
32. 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(6):442–7.
33. Gruber SA, Sagar KA, Dahlgren MK, Racine M, Lukas SE. Age of onset of marijuana use and executive function. Psychol Addict Behav. 2012;26(3):496–506.
34. Gruber SA, Silveri MM, Dahlgren MK, Yurgelun-Todd D. Why so impulsive? White matter alterations are associated with impulsivity in chronic marijuana smokers. Exp Clin Psychopharmacol. 2011;19(3):231–42.