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Long-Term Effects of Prenatal Cannabis Exposure: Pathways to Adolescent and Adult Outcomes

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Abstract

With the increased prevalence, potency, and acceptability of cannabis use during pregnancy, it is important to understand the developmental effects of prenatal cannabis exposure (PCE). This review discusses methodological considerations for studies of PCE, including the assessment of exposures, covariates, and outcomes, and reviews findings from prospective, longitudinal studies of PCE. There is some evidence for associations between PCE and restricted growth at birth, but not for long-term effects on growth. PCE appears to have subtle yet enduring effects on memory and achievement in children and adolescents. Despite differences in sample demographics and measurement, there are remarkably consistent effects of PCE on externalizing behaviors, such as delinquency and substance use, which persist into adulthood. Longitudinal analyses demonstrate the importance of early cannabis initiation for pathways between PCE and adult functioning, including substance use and abuse, memory deficits, and psychotic symptoms. Animal studies demonstrate direct effects on the development of the brain via activation of endogenous endocannabinoid systems. Cannabis-induced activation of the endocannabinoid system causes alterations in the release of neurotransmitters and the modulation of brain plasticity in neural pathways that underlie cognition, motivation, and behavior regulation. Future research should consider cannabis use before pregnancy, the timing and route of exposure, polysubstance exposures, and inter-generational effects.

Keywords

cannabis; marijuana; prenatal; gestational

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1. Introduction

Data on prenatal cannabis use from the 2000s onward document an increase in its prevalence (Agrawal et al., 2019; Brown et al., 2017; Young-Wolff et al., 2019), with 12% of pregnant American women reporting past month use during their first trimester (Volkow et al., 2019). Pregnant women perceive cannabis use as more acceptable and less risky (Bayrampour et al., 2019; Jarlenski et al., 2017) as the U.S. legal climate increases access to medical and recreational cannabis (Chiu et al., 2021). Women who live in states that have legalized recreational cannabis use are more likely to use cannabis before, during, and after pregnancy than those who live in states that have not legalized recreational use (Gnofam et al., 2020; Skelton et al., 2020, Taylor et al., 2021), especially if they live close to a cannabis retailer (Young-Wolff et al., 2021). Evidence from seized marijuana samples indicates that cannabis potency has also increased, with an increase in the ratio of Δ9-tetrahydrocannabinol (THC) to cannabidiol and correspondingly greater psychoactive effects (Cascini et al., 2012; Chandra et al., 2019; ElSohly et al., 2016, 2021). Although some pregnant women voice concerns about the possible effects of prenatal cannabis exposure (PCE) on children, or about the legal ramifications of their use, many women describe it as “safe and natural” and prefer smoking herbal cannabis to medications prescribed by their physicians (Chang et al., 2019; Vanstone et al., 2021). This review focuses on the available evidence for the long-term effects of PCE from prospective cohort studies, with brief sections on methodological issues and neurobiological mechanisms.

2. Methodological issues in the study of PCE

The teratologic model is the primary theoretical framework guiding methodology in studies of PCE, including the measurement of PCE, covariates, and developmental sequelae. The main principles of the teratologic model are: effects across outcome domains are a function of the dose, with lower doses leading to central nervous system (CNS) effects in the absence of morphologic changes; effects within a domain are a function of dose and duration of exposure; effects are related to the stage of pregnancy during which they occur; they may not be manifested until later in development (sleeper or latent effects); and they are a function of both the teratogenic exposure and the environment in which the organism is raised (environmental effects can be independent or interactive) (Vorhees, 1989). Thus, it is crucial to assess the dose and duration of PCE, consider the gestational timing, follow exposed individuals past infancy, and measure intrauterine and postnatal environments. Developmental psychopathology is another model that is used to frame the long-term effects of prenatal exposures. This perspective highlights the importance of early exposures for outcomes later in life, a focus on risk and protective factors in causal processes, continuities and discontinuities between normal and pathological, and variability in outcomes from the same exposures (Rutter & Sroufe, 2000). The developmental psychopathology framework prioritizes prospective cohort studies that examine many outcomes so that it is possible to trace pathways from early exposures to a variety of different consequences.

The major focus of this review is not an in-depth examination of methodological issues in the field (interested readers should consult references cited in this section for further details, e.g., Jacobson & Jacobson, 2005; Richardson et al., 2006). Here we will briefly

review several methodological concerns to highlight issues to be evaluated when comparing findings from different cohort studies. Among the methodological considerations when evaluating the effects of PCE, the first critical issue is the assessment of the exposure. The *Cannabis Sativa* plant consists of more than 500 compounds and more than 100 cannabinoids, with Δ9-THC being the primary psychoactive ingredient (ElSohly & Gul, 2014). There are different forms and modes of use of cannabis, with the most common being smoking dried cannabis (Schauer et al., 2020). In the U.S., the most commonly combusted forms of cannabis include bongs, pipes, joints (rolled in cigarette paper), and blunts (rolled in tobacco leaves or hollowed little cigars) (Hindocha et al., 2016). In other parts of the world, spliffs (a combusted mixture of cannabis and tobacco) are more common (Hindocha et al., 2016; Smith et al., 2020). Although less prevalent, other modalities, such as vaping, dabbing marijuana wax, or ingestion of food products made with cannabis/THC (candy, brownies, rice cereal treats), are more common in states with legalized recreational cannabis (Schauer et al., 2020). Given the variety of products and types of ingestion, THC levels can vary widely leading to differences in exposure levels. It is thus critical to ask specific questions about the type and mode of cannabis use to accurately assess prenatal exposure.

A variety of parameters are key for accurately assessing exposure; quantity, frequency, duration, and dose. These are easiest to assess with drugs such as tobacco and alcohol that are federally regulated and have consistent and measurable amounts of active ingredients. Use is more difficult to assess with other drugs, such as cocaine and cannabis, where active ingredients vary with source, method of preparation, and modality of use. Assessment of use can occur through self-report, interviews, and biological assays. There is substantial evidence of greater detection of cannabis use by self-report/interview methods than by biological assays when questions are detailed and understandable and when interviewers are carefully trained (El Marroun et al., 2011b; Fendrich et al., 2004; Gray et al., 2010; Oga et al., 2020; Richardson et al., 2006). Biomarkers vary in their effectiveness at detecting recent cannabis use, depending on the type of sample provided. Urine is the most commonly used bioassay and has a relatively long window of detection (from several days up to ~30 days), although it is more likely to detect chronic, heavy cannabis use rather than intermittent or light cannabis use. Meconium (Gray et al., 2010) and umbilical cord (Metz et al., 2022) assays may only detect PCE from the last trimester and month of pregnancy, respectively, but cannabis use is most common during the first trimester (see Richardson et al., 2006 for a more detailed discussion of types of assays and their strengths and limitations). The accurate detection of use via self-report will depend on the characteristics of the sample, as well as the purpose of the questions, with mis-reporting more likely to occur in clinical samples and in those with no prenatal care (Holland et al., 2016; Richardson et al., 1999). Pregnant women are not universally screened for prenatal drug use, leading to selection bias in studies relying on medical record data to investigate the effects of PCE.

A second methodological consideration is the assessment of covariates that are associated with PCE and child outcomes such as other pre- and postnatal drug use (including alcohol and nicotine), sociodemographic characteristics, medical history, psychological characteristics, and the home environment (Day et al., 2006; Goldschmidt et al., 2004). These covariates must be assessed with similar precision as the main exposure of interest (Jacobson & Jacobson, 2005). Failure to consider the effects of these characteristics will

lead to a misattribution of the effects of the prenatal exposure (Fried, 2002b; Richardson & Day, 1994). For example, a study focused on the effects of prenatal cocaine exposure on adolescent executive function (EF) found an independent effect of prenatal cannabis exposure on EF, even after parsing out the effects of prenatal tobacco, alcohol, and cocaine exposure (Karpova et al., 2021). Without measuring these other prenatal exposures, the authors may have concluded that prenatal cocaine exposure was the only teratogen involved in the EF deficit.

A third methodological consideration is the assessment of outcomes. This will be determined by the domains of the theoretical model framing the research (e.g., the teratologic model) and by the desire to test direct, moderating, and mediating models that result from the teratologic principles. According to the developmental psychopathology framework, it is important to test multiple outcomes because the same exposure may manifest differently in separate individuals (Rutter & Sroufe, 2000). However, the wide variety of assessments used for different covariates and outcomes by various research groups further complicates the comparison of effects of PCE across studies. This variability in measurement and assessment of covariates and outcomes may lead to conflicting reports on the effects of PCE.

3. Effects of PCE on offspring development from infancy through adulthood

There are three primary outcome domains that have been investigated in prospective, longitudinal studies of PCE: growth, CNS/cognitive development, and behavior, consistent with the principles of the teratologic model.

3.1. Growth

There were few reported effects of PCE on offspring growth in the earliest longitudinal studies that had detailed measures of quantity and frequency of prenatal cannabis use. These include the Ottawa Prenatal Prospective Study (OPPS), a study of 700 low-risk women recruited from 1979 to 1983 from prenatal clinics across Ottawa, Ontario (Canada) and the Maternal Health Practices and Child Development (MHPCD) project, a study of 829 at-risk women recruited early in pregnancy from 1982 to 1985 from a hospital prenatal clinic in Pittsburgh, PA (U.S.A.). In the OPPS, there were no effects of PCE on growth from birth through 24 months of age (Fried & O'Connell, 1987), but offspring with PCE had reduced head circumference at the 9- to 12-year follow-up (Fried et al., 1999). In the MHPCD, a cohort characterized by social disadvantage, PCE was associated with reduced length at birth, with no evidence of morphological changes associated with PCE (Day et al., 1991), and no relations between PCE and growth during childhood (Day et al., 1992, 1994a). These results are further corroborated by the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC), in which 12,000 pregnant British women were mailed questionnaires between 1991–1992. There was no effect of PCE on birth weight, length, or head circumference, after controlling for demographic background and other prenatal substance use in the ALSPAC (Fergusson et al., 2002). Several meta-analyses of data from this period have highlighted inconsistencies in relations between PCE and growth due to differences in measures of PCE

and inclusion of covariates, especially prenatal tobacco exposure (Conner et al., 2016; Gunn et al., 2016).

In more recent cohort studies, PCE was associated with reduced birth weight even after controlling for prenatal tobacco exposure (El Marroun et al. 2009; Gabrhelík et al., 2021; Haight et al., 2021). These include Generation R, a prospective study of 9,778 pregnant women recruited from 2002 to 2006 in the Netherlands, and the Norwegian Mother and Child Cohort Study (MoBa), a population-based cohort of over 95,000 women recruited from 1999 to 2008. In the Adolescent Brain Cognitive Development (ABCD) study of 11,875 American children born between 2005 and 2009, there was an effect of retrospectively-measured PCE on birth weight, but this effect became marginally significant after adjusting for covariates and correcting for multiple tests (Paul et al., 2021). The prevalence of PCE was lower in the European studies (1–3%) and, in all of the more recent large cohort studies, no data are available on quantity or frequency of the exposure. Data on the frequency of prenatal cannabis use are available for some American states in the Pregnancy Risk Assessment Monitoring System (PRAMS). Analyses of PRAMS data from 2017 onward revealed that more frequent PCE (defined as at least once a week) predicted low birth weight (LBW) and small-for-gestational age (SGA) (Haight et al., 2021; Nguyen & Harley, 2022). Similarly, secondary data analyses of hospital records have demonstrated that infants born to mothers with a cannabis-related diagnosis were more likely to be LBW and SGA (Bandoli et al., 2021; Oni et al., 2022; Shi et al., 2021). It is possible that the increased potency of cannabis being used currently may result in greater effects on growth than those seen in the older cohorts.

3.2. CNS/Cognitive Development

For the second domain, similar measures were used to measure CNS and cognitive development in the MHPCD and OPPS, allowing for comparison of findings. During infancy, the MHPCD group reported that PCE was associated with changes in sleep cycling and motility at birth (Scher et al., 1988). In the OPPS, Fried and Makin (1987) reported increased tremors and startles on the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) at birth; however, this finding was not replicated in the MHPCD cohort using the same scale (Richardson et al., 1989). PCE was associated with lower Bayley Scales of Infant Development (BSID) Mental Development Index scores in the MHPCD at 9 months but not at 19 months (Richardson et al., 1995), and not with the BSID scores in the OPPS at 12 or 24 months (Fried & Watkinson, 1988). Across both cohorts, there was some evidence for differences in neonatal behavior, but inconsistent effects on cognitive tests from ages 9 to 24 months. These inconsistencies may be due to differences in study design and measurement: MHPCD participants were not only higher-risk due to lower SES, but they were all recruited early in pregnancy and trimester-specific data on PCE were analyzed. By contrast, only 28% of the OPPS participants were recruited in the first trimester, when cannabis use is more common (Volkow et al., 2019), and OPPS investigators analyzed average PCE across pregnancy rather than trimester-specific effects.

During childhood, in the MHPCD Project, there were consistent negative relations with PCE and cognitive and CNS outcomes, including sleep disturbances at 3 years (Dahl et al., 1995),

decreased IQ and memory scores at 3 (Day et al., 1994b) and 6 years (Goldschmidt et al., 2008), and lower memory scores at 10 years (Richardson et al., 2002). Sleep disturbances were also reported at 3.5 years of age (Murnan et al., 2021) in the smaller Lifestyle and Early Achievement in Families (LEAF) cohort that was recruited more recently from high-risk obstetric clinics for the Ohio Perinatal Research Network's Perinatal Research Repository (Klebanoff et al., 2020). Attention deficits, but not lower global IQ scores, were reported for 48-month-old children with PCE in a secondary analysis of data of two randomized control trials from 2006–2009 (Smid et al., 2022). The OPPS reported mixed findings in their lower risk cohort, with detrimental associations between PCE and memory at 3 to 4 years of age (Fried & Watkinson, 1990), no effects on memory at 5 to 6 years of age (Fried et al., 1992a) or on IQ and memory at 6 to 9 years (O'Connell & Fried, 1991), and detrimental effects of PCE on verbal reasoning and EF at 9 to 12 years (Fried et al., 1998). Symptoms of sleep disturbance were seen in 9- to 11-year-olds with retrospectively measured PCE in one analysis of the ABCD cohort (Winiger & Hewitt, 2020), but these disappeared after adjustment for covariates in another analysis (Paul et al., 2021). During adolescence, in the OPPS at 13 to 16 years of age, Fried & Watkinson (2001) reported that PCE was associated with poorer stability of attention to tasks, but not with other aspects of attention such as focusing and encoding, and with deficits in visual memory and poorer spelling recognition (Fried et al., 2003). In the MHPCD, at 16 years of age, PCE was associated with poorer interhemispheric motor coordination as measured by the Bimanual Coordination Task (Willford et al., 2010). Overall, effects of PCE on childhood cognitive development and CNS outcomes appear to be more evident in higher-risk samples and in specific domains of attention and memory rather than in global IQ.

Similarly, there are mixed results for PCE and academic achievement. In the MHPCD, PCE was associated with lower academic achievement at ages 10 (Goldschmidt et al., 2004) and 14 (Goldschmidt et al., 2012). At age 14, this deficit was fully mediated by the earlier effects of PCE on child IQ, attention problems, and early initiation of cannabis use (Goldschmidt et al., 2012). PCE was not associated with academic achievement during childhood in the lower-risk OPPS sample (Fried et al., 1997; Fried & Smith, 2001). It is possible that only PCE individuals who develop in less than optimal environments will experience lower academic achievement. According to the "double hit" hypothesis, prenatal cannabis use strikes the first blow to the fetal endogenous cannabinoid signaling system, rendering it more vulnerable to environmental stressors (Richardson et al., 2016), consistent with a teratologic model. In a large Australian data linkage study of children born between 2003–2005, those offspring whose mothers had a documented prenatal diagnosis of Cannabis Use Disorder (CUD) were less likely than those whose mothers did not have CUD to meet the national standard on standardized tests of spelling, grammar, and writing in grades 3, 5, 7, and 9 (Betts et al., 2021). The offspring in this study may have been exposed to more frequent and/or higher doses of prenatal cannabis, on average, than the offspring from the MHPCD or OPPS, given their mothers' CUD diagnosis. This is also consistent with teratologic principles (dosage and interaction with the environment will determine outcomes associated with prenatal exposures).

In the MHPCD Project, Willford et al. (2021) reported that there was no direct effect of PCE on memory at 22 years of age; however, there were indirect effects through childhood

intelligence and memory and early onset of cannabis use during adolescence. That is, the effects of PCE evident during childhood and adolescence resulted in prenatally-exposed adults who were more likely to experience deficits in memory. By contrast, there were no relations between PCE and IQ at 17 to 20 years of age in the lower-risk OPPS sample (Fried et al., 2002c). According to the developmental psychopathology principle of multi-finality, individuals with the same risk factor may experience different outcomes. Long-term CNS/cognitive effects may only emerge at higher doses of PCE and/or in combination with postnatal stressors and early postnatal exposure to cannabis (Fried, 2002b; Richardson et al., 2016). As described by both the double-hit hypothesis and teratologic model, prenatal dose and interactions with the environment are likely to moderate the effects of prenatal exposures on development.

3.3. Behavior

The third domain of behavioral outcomes can be divided into internalizing (i.e., withdrawn, anxious, depressive symptoms) and externalizing (i.e., aggressive, delinquency, hyperactivity, inattentive symptoms) behavior problems. There are very few reports of relations between PCE and internalizing behavior problems. PCE was associated with increased child-reported depressive symptoms (Gray et al., 2005) and with high levels of combined depression/anxiety symptoms (Leech et al., 2006) at 10 years of age in the MHPCD. This finding was not replicated at other ages or in most other cohorts. However, PCE was associated with increased social withdrawal in a small sample of preschoolers from the LEAF cohort (Murnan et al., 2021). These results are based on a subsample of LEAF with only 15 PCE offspring (Murnan et al., 2021), but as the exposures were more recent (2010–2016), they reflect more contemporary forms of cannabis exposure in a high-risk sample (Klebanoff et al., 2020). As with the findings on cognitive development and consistent with current theoretical models, these results suggest that there may be an effect of PCE on childhood internalizing symptoms in the most vulnerable exposed children that may not occur in other exposed children.

By contrast, there is extensive evidence of associations between PCE and externalizing behavior problems and symptoms of psychosis across several prenatal cohorts. In the MHPCD, PCE was associated with more errors of commission, an indication of impulsivity, but with fewer omission errors, an indication of better attention, at the 6-year follow-up (Leech et al., 1999). At age 10, there was increased caregiver-reported impulsivity, activity, inattention, and delinquency (Goldschmidt et al., 2000) and at age 14, increased delinquent behaviors (either caregiver- or child-reported) (Day et al., 2011). In the OPPS, PCE was also associated with increased omission errors on a laboratory task and increased caregiver-reported hyperactivity at 6 years (Fried et al., 1992b) and with laboratory measures of attention at 13 to 16 years (Fried & Watkinson, 2001). However, these were not seen in the OPPS at 9 to 12 years (Fried et al., 1998). In the Generation R cohort, PCE was associated with maternal reports of increased aggression and inattention in 18-month old girls (El Marroun et al., 2011a), no effects on mother-reported behavior at age 3 (Huizink, 2014), increased teacher- and child-reported externalizing problems at ages 7 to 9 (El Marroun et al., 2019), and increased child-reported psychotic-like symptoms (such as hearing voices or seeing things other people don’t see) at age 10 (Bolhuis et al., 2018). Similarly, in 9-

to 11-year-olds in the ABCD study, PCE was associated with more child-reported psychotic-like symptoms, inattention during an inhibition task, and caregiver-reported externalizing behavior problems (Paul et al., 2021). Day et al. (2015) reported that both PCE and early onset of cannabis use were independently associated with self-reported psychotic symptoms at the 22-year follow-up in the MHPCD. In sum, despite differences in sampling frames and measures, research groups in different countries have reported that PCE is associated with externalizing behavior problems and psychotic symptoms across childhood and adolescence.

An important behavioral outcome associated with externalizing problems and linked to PCE is offspring substance use. In the MHPCD, PCE predicted cannabis use by age 15 (Day et al., 2006) and frequency of cannabis use at age 22 (Sonon et al., 2015). Early onset of cannabis was part of a pathway to long-term outcomes in this cohort, linking PCE to lower academic achievement at age 14 (Goldschmidt et al., 2012), poorer adult functioning (educational attainment, work status, arrest history) (Goldschmidt et al., 2016), daily dual use of cannabis and tobacco by age 22 (De Genna et al., 2021), and CUD (Sonon et al., 2016). There is also converging evidence of long-term effects of PCE on risk for substance use and abuse in the OPPS. Porath and Fried (2005) found that PCE was associated with initiation of cannabis use by the 16- to 21-year follow-up (mean age = 18 years) among males, but not females. There is no corresponding sex difference in the MHPCD. To date, no other groups with prospective cohort data have examined the effects of PCE on frequency of cannabis use, polysubstance use, or CUD.

Statistical modeling of mediator and indirect effects in the MHPCD cohorts highlights the particular importance of early cannabis initiation among those with PCE, controlling for prenatal tobacco and other exposures, including cumulative environmental risks. Goldschmidt et al. (2012) found that the effect of PCE on academic achievement was mediated by the earlier effects of PCE on child IQ, attention problems, and early initiation of cannabis use. Other reports from the MHPCD have also delineated pathways from PCE to young adult daily dual use of cigarettes and cannabis (De Genna et al., 2021) and CUD (Sonon et al., 2016) via early adolescent cannabis use. Thus, individuals prenatally exposed to cannabis are more likely to initiate cannabis during another key period of brain development - early adolescence - and offspring with this dual exposure are more likely to experience a myriad of negative outcomes related to cognitive function, including adult memory deficits (Willford et al., 2021), psychotic symptoms (Day et al., 2015), and indicators of poorer adult functioning such as unemployment, arrests, and lower educational attainment (Goldschmidt et al., 2016). This is consistent with the “double hit” hypothesis of PCE in which the prenatal exposure “softens” or primes the endogenous cannabinoid signaling system, resulting in an individual that may be more susceptible to environmental stressors. Results of clinical functional magnetic resonance imaging (fMRI) studies in prenatal cohorts indicate that PCE alters brain activity related to response inhibition, even if it is not consistently related to performance on executive functioning tasks (Longo et al., 2013; Smith et al., 2004; 2016). Altered brain activity may represent subtle deficits in executive functioning that underlie the long-term behavioral differences seen in exposed adolescents and adults, such as early and persistent substance use, as detailed in the next section.

3.4. Neuroimaging studies linking brain function and behavior

Several fMRI studies from the OPPS confirm what has been found on the behavioral neuropsychological assessments used in the MHPCD and OPPS, with PCE-associated changes in brain activation and function. fMRI results indicate long-term, subtle effects of PCE on the neural circuitry that supports cognitive functions including response inhibition (Smith et al., 2004) and visual-spatial working memory (Smith et al., 2006), demonstrating an overall negative impact on EF (Smith et al., 2016). A pattern emerges across these imaging studies of no behavioral differences on performance of the cognitive tasks, but alterations in brain activity for the recruitment of additional brain regions and more extensive activation to complete the tasks in exposed than in unexposed individuals. In addition, a recent study showed widespread PCE-related functional connectivity differences including connections between dorsolateral, medial and superior frontal, insula, anterior temporal, and posterior cingulate cortices, regions associated with the function of the hippocampus and memory processing (Thomason et al., 2021). These few studies suggest that PCE may require adaptive responses that include the need for additional neural resources to achieve normal behavioral performance of cognitive tasks. Taken together, PCE effects were detected in brain function in young adults, demonstrating long-term alterations in brain function associated with cognitive performance.

The impact of developmental cannabis exposure is also evident in fMRI studies that control for PCE in adolescent cannabis users. Functional neuroimaging studies conducted by the OPPS showed an association between adolescent onset of heavy use and the recruitment of additional brain regions while performing tasks that require response inhibition, such as a cognitive Stroop task (Hatchard et al., 2014) and a visual-spatial working memory task (Smith et al., 2010). The OPPS also reported a dose-dependent association between young adult cannabis use and neural function during response inhibition, after controlling for prenatal and adolescent cannabis exposure (Smith et al., 2011). Further, fMRI data from the MHPCD showed that decreased brain activation in the right posterior parietal cortex mediated the association between early onset cannabis use and longer reaction times during encoding processes of working memory. This association was independent of frequency of cannabis use and implicates pre-onset factors such as PCE that predict the development of cognitive behavior and brain function, as well as the initiation of substance use (Tervo-Clemmens et al., 2018a).Thus, the results of fMRI studies from the two prenatal cohort studies that have studied offspring into adulthood indicate that there are risks associated with cannabis exposure during key developmental periods of brain development (gestation, adolescence), as well as with current cannabis use.

3.5. Summary: Evidence for the effects of PCE

Briefly, there is some evidence for associations between PCE and restricted growth at birth, especially in more recent cohorts, but not for long-term effects on offspring growth. By contrast, PCE appears to have subtle, long-term effects on memory and achievement and consistent, persistent relations have been found between PCE and externalizing behaviors (such as delinquency and substance use) and psychotic symptoms. These effects persist in multivariate analyses controlling for maternal characteristics and the home environment. The use of prospective, longitudinal analyses revealed effects of PCE on adult functioning

and the importance of early cannabis initiation for pathways to young adult substance use and abuse, memory deficits, psychotic symptoms, and adult-role functioning, including employment and educational attainment. The results of the neuroimaging studies of prenatally exposed individuals who also used cannabis during adolescence showed that early adolescent cannabis exposure may lead to limitations or delayed development of brain circuitry that underlies cognitive function. It is also possible that more prolonged cannabis exposure during adulthood may be required to observe the cognitive effects of early-onset cannabis use (Tervo-Clemmens et al., 2018b). Imaging studies in young adults from the OPPS show PCE-related changes in brain activation in the inferior and middle frontal gyrus, hippocampal regions, left occipital, and cerebellum while performing a visual-spatial working memory task (Smith et al., 2006) and changes in brain activation in the left postcentral gyrus, left cuneus, and lingual gyrus while performing tasks that require response inhibition (Smith et al., 2016). These studies considered prenatal, adolescent, and current cannabis use, and underscore that effects of PCE on behavior and brain function should always be interpreted in the context of potential exposures in other developmental periods. As a whole, this literature highlights the importance of longitudinal cohort studies to fully understand the long-term effects of PCE.

4. Neurobiological mechanisms underlying effects consistent with that seen in human samples

The use of and prenatal exposure to cannabis lead to activation of the endogenous endocannabinoid system (eCB). Receptor activity within the eCB is modulated by anandamide and 2-arachidonoyl glycerol, which are produced on demand in response to brain activity and function to modulate homeostasis, neural signaling, and metabolic pathways. In the CNS, there are two types of cannabinoid receptors. The cannabinoid receptor 1 (CB_1) is a G-protein-coupled receptor that is widely expressed throughout the adult brain and functions to modulate the release of other neurotransmitters including GABA, glutamate, and acetylcholine. The cannabinoid receptor 2 (CB_2) is expressed primarily in the periphery, but is also expressed in the CNS and is important for modulating neuroimmune and neuroinflammatory responses (Chen et al., 2017; Van Sickle et al., 2005). CB_1 receptors are detected at 14 weeks gestation and density increases in hippocampal, frontal cortex, basal ganglia, and cerebellum prenatally to adulthood (Fride, 2008). The effects of cannabinoids are mostly mediated by activation of CB_1 and CB_2.

Understanding the mechanisms that underlie the impact of PCE on the developing brain is important given that the brain is undergoing rapid development from the prenatal period extending into young adulthood. The eCB is present in reproductive tissues, including the placenta (Park et al., 2003), is found early in brain development around gestational day 11–14 in rats (Berrendero et al., 1998, 1999) and around 19 weeks gestation in humans (Mato et al., 2003), and the overall expression of CB_1 is much higher prenatally compared to the mature brain (Berrendero et al., 1998; Mato et al., 2003). Alterations in eCB function in the placenta may underlie increased reports of PCE-related risks for pregnancy complications, including SGA, preterm birth, and stillbirth (Luke et al., 2019) by reducing cell viability and proliferation and increasing oxidative stress and apoptosis

(Martínez-Peña et al., 2021). The eCB system functions in a regulatory role in all aspects of brain development including determining cell fate and neuron proliferation, migration, and differentiation (Grant et al., 2018). The development of brain systems that function in motivation, cognition, emotion and behavior regulation, and reward processing are directly impacted by PCE. Neuroimaging studies corroborate changes in brain function associated with PCE and cognitive function (Smith et al., 2006; Smith et al., 2016; Tervo-Clemmens et al., 2018a; Tervo-Clemmens et al., 2018b). MRI evaluations are important given that the endogenous endocannabinoid systems are involved in brain development and are directly impacted by PCE. The effects of THC on the function of the eCB during early development are hypothesized as the primary underlying mechanism for the protracted effects of PCE on fetal growth, cognitive function, and behavior/mental health.

Chronic activation of CB_1 due to PCE impacts the gene expression and function of multiple neurotransmitters and receptors including dopamine (Jutras-Aswad et al., 2009). The functioning of the mesocorticolimbic system is regulated by dopamine and its receptors are involved in developmental differentiation and circuit formation of the forebrain (Frederick & Stanwood, 2009). The effect of PCE on dopamine function during early brain development has been linked to alterations in cognitive function and vulnerability to substance use disorders as expressed in rodent models (Ross et al., 2015; Renard et al., 2017). In early brain development, CB_1 receptors mediate the actions of Δ9-THC that are predominantly expressed within mesocorticolimbic brain structures, including the nucleus accumbens and ventral tegmental area. In utero THC exposure alters the function of dopamine receptors (Grant et al., 2018) and increases the general responsiveness of the mesocorticolimbic dopamine system (Hurd et al., 2019). The interaction of THC with the mesocorticolimbic system is implicated in substance use disorders and provides a mechanism through which in utero and/or adolescent exposure to THC increases vulnerability to substance use disorders later in life, as shown in human work (Day et al., 2006; Porath & Fried, 2005; Sonon et al., 2015).

The effect of pre- and perinatal cannabis exposure on the development of the prefrontal cortex (PFC), amygdala, and hippocampus, key structures for the performance of cognitive functions, is also demonstrated in animal models (Dow-Edwards & Silva, 2017). PCE affects behaviors associated with the PFC including emotion regulation, memory, and social behaviors (Trezza et al., 2012). The eCB system plays an important role in the development of cognitive behaviors by modulating plasticity through changes in the function of both GABA and glutamate transmitter systems (Dow-Edwards & Silva, 2017). GABA is stimulated by the activation of CB_1 and is the primary inhibitory neurotransmitter in the brain. Vargish et al. (2017) showed that maternal treatment with the cannabinoid agonist WIN55,212-2 leads to a loss of interneurons, decreased synaptic plasticity, and changes in feedforward and feedback inhibition in the hippocampus of offspring. These circuitry changes are associated with alterations in the responsiveness of neurons to excitatory and inhibitory inputs. In addition, these effects were associated with alterations in social behavior. Consistent with the animal models, changes in behavior regulation and cognitive function are reported in children and adolescents with PCE (Fried, 2002a; Fried et al., 1998; Goldschmidt et al., 2000; 2004; 2008; 2016).

5. Future research directions

The three large longitudinal cohorts that enrolled women prenatally (MHPCD, OPPS, Generation R) also collected a variety of important sociodemographic, environmental, and substance use characteristics that are associated with PCE and offspring outcomes, and thus were able to control statistically for important covariates of cannabis use and developmental outcomes. However, exposure to structural racism and discrimination (Cohodes et al., 2019; Seaton et al., 2018; Williams et al., 2019) and violence (Frank et al., 2011; Mueller & Tronick, 2019) are currently understudied and should be included in future research, given the pervasiveness of these experiences (Finkelhor et al., 2015; Kapaya et al., 2019; Nagata et al., 2021; Pachter et al., 2010). It may also be important to consider substance use prior to pregnancy and paternal/partner cannabis use. For example, Bolhuis et al. (2018) reported that the effects of PCE on psychotic-like symptoms were significant only when pre-conception and prenatal cannabis use were combined into one variable. Further, El Marroun et al. (2019) reported that maternal cannabis use before pregnancy, maternal tobacco smoking during pregnancy, and paternal cannabis use were all associated with externalizing behavior problems, indicating a possible shared genetic and environmental influence on child behavior problems. Suggestions to focus on windows of exposure and paternal exposure have also been made in a review of the animal literature (Lee & Hardy, 2021). Future research will also need to carefully consider the developmental implications of polysubstance exposures. The link between PCE and exposure to other common substances such as nicotine and alcohol is well-documented (Coleman-Cowger et al., 2017; Ko et al., 2020; Obisesan et al., 2020; Qato et al., 2020). Co-exposure may be more common in states where recreational cannabis use is legal (Skelton et al., 2021) and recent work highlights the amplifying effects of co-exposures (Breit et al., 2019a, 2019b; De Genna et al., 2019; Eiden et al., 2020; Nguyen & Harley, 2022).

Different study designs are warranted to provide a more complete picture of the developmental effects of PCE. Surveillance studies with nationally representative data are needed to provide the latest estimates of prevalence of PCE with enough power to reveal the effects of PCE on less common outcomes, although data are often limited to dichotomous “any/none” variables for PCE and important covariates such as prenatal tobacco use. Prospective, longitudinal cohort studies have smaller samples but collect fine-grained data on the quantity and frequency of different exposures that are key to detecting dose-response or threshold effects of PCE on development. It is also important to examine different preparations and routes of administration for PCE because of the popularity and vascular effects of combustible cannabis use and the higher levels of THC associated with certain products such as cannabis concentrates and synthetic cannabis, which may have implications for developmental outcomes. Research on smaller samples examining mother-child interactions has demonstrated indirect effects of PCE on child functioning via caregiver behavior (Eiden et al., 2018; Schuetze et al., 2019). New longitudinal data are needed to trace pathways from more recent exposures to PCE with higher levels of THC seen today on long-term outcomes across developmental stages and lifespan transitions. Although the ABCD study only has retrospective maternal reports of PCE, collection of baby teeth may eventually allow for objective measurement of the timeline of PCE in these

individuals (Uban et al., 2018). Qualitative research is also necessary to better understand the context within which PCE occurs and to center the experiences of individuals who choose to use cannabis before, during, and after pregnancy. Triangulating data from various sources (e.g., structured and qualitative interviews, biological samples, medical record) will allow for a more comprehensive assessment of exposures and their effects on development. In the future, research on epigenetics and inter-generational effects will continue to improve our understanding of how cannabis exposure shapes development over time (Bara et al., 2021; Lee & Hardy, 2021). Future studies examining the impact of THC exposure through breast milk are warranted because endocannabinoids are present in breast milk (Martin, 2020), and studies report infant feeding issues related to suck/swallow during breastfeeding (Barbosa-Leiker et al., 2021; Brown et al., 2018). Animal studies have shown that CB_1 receptor activation plays an important role in suckling and milk intake by initiating the suckling response (Fride, 2008). It will be important to consider the long-term epigenetic impact of cannabis exposure at key developmental time points. Studies are limited at this time, but the interactions between exposure to cannabis and environmental factors have the potential to influence the expression of genes throughout the lifespan and across generations, affecting behavior and risk for disease.

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Highlights

- PCE may impact fetal growth, with no evidence of long-term effects on size.
- Subtle effects on cognition are supported by neuroimaging and rodent studies.
- PCE is associated with direct effects on behavior and brain function.
- PCE has indirect effects on adult functioning via early initiation of cannabis use.