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The First "Hit" to the Endocannabinoid System? Associations Between Prenatal Cannabis Exposure and Frontolimbic White Matter Pathways in Children

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ABSTRACT

BACKGROUND: Cannabis is the most used federally illicit substance among pregnant people in the United States. However, emerging preclinical data show that a significant portion of cannabis constituents, such as Δ^9-tetrahydrocannabinol and its bioactive metabolites, readily cross the placenta and accumulate in the fetal brain, disrupting neurodevelopment. Recent research using the Adolescent Brain Cognitive Development (ABCD) Study cohort has linked prenatal cannabis exposure (PCE) to greater neurobehavioral problems and lower total gray and white matter volume in children. Here, we examined the impact of PCE on frontolimbic white matter pathways that are critical for cognitive- and emotion-related functioning, show a high density of cannabinoid receptors, and are susceptible to cannabis exposure during other periods of rapid neurodevelopment (e.g., adolescence).

METHODS: This study included 11,530 children (mean ± SD age = 118.99 ± 7.49 months; 47% female) from the ABCD Study cohort. Linear mixed-effects models were used to examine the effects of caregiver-reported PCE on fractional anisotropy of 10 frontolimbic pathways (5 per hemisphere).

RESULTS: PCE was associated with lower fractional anisotropy of the right ($\beta = -0.005$, $p < .001$) and left ($\beta = -0.003$, $p = .007$) fornix, and these results remained significant after adjusting for a variety of covariates, multiple comparisons, fractional anisotropy of all fibers, and using a quality-control cohort only.

CONCLUSIONS: In sum, we demonstrated small, yet reliable, effects of PCE on white matter integrity during childhood, particularly in the fornix, which plays a crucial role in emotion- and memory-related processes. Future studies are needed to understand the impacts of small changes in brain structure or function on neurodevelopment and risk of neurobehavioral problems.

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Cannabis is the most frequently used federally illicit substance among pregnant people in the United States (1). Survey research shows that rates of cannabis use among pregnant individuals more than doubled between 2002 (3.4%) and 2017 (7%), and rates are highest among young people (up to 22%; ages 18–25 years) (2–4). Many people report using cannabis to combat the negative symptoms associated with pregnancy (e.g., anxiety, nausea/vomiting, and sleep disturbances) (3,4). Individuals report more frequent cannabis use during the first trimester—coinciding with early pregnancy symptoms—compared with the second and third trimesters (5). Furthermore, although symptoms associated with pregnancy can emerge as early as 2 weeks into gestation, many individuals remain unaware of their pregnancy until about 6 weeks (6). The rising popularity of cannabis use accompanied by reduced perceptions of cannabis risk (7) and increased psychoactive Δ^9-tetrahydrocannabinol (THC) potency (8) have amplified public health concerns regarding the adverse effects of prenatal cannabis exposure (PCE) on neurodevelopment.

Due to their lipophilic nature, cannabis constituents, such as THC, can easily cross through the placenta and deposit into the fetal brain. Our previous rodent study, using an inhalation model of cannabis during pregnancy, demonstrated that THC and its metabolites accumulate in the placenta, with 30% of circulating THC accumulating in the fetal brain (9). THC binds to cannabinoid type 1 (CB_1) receptors, which are expressed in the brain as early as 5 weeks into fetal development (10); therefore, PCE during gestation may impact the developing endocannabinoid (eCB) system. During gestation, CB_1 receptors play an initial role in influencing neuronal progenitor cells and axonal growth and then continue to modulate several neuronal processes (e.g., synaptogenesis, myelination) throughout fetal development and into adolescence (11,12).

Importantly, during embryonic development, CB_1 receptors exhibit a unique enrichment in white matter tracts, indicating

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that cannabinoid signaling may be capable of influencing the development of white matter during early developmental stages (13,14). CB_1 receptors continue to increase in density from fetal development through childhood and adolescence (15); however, there is a notable developmental shift in the localization of these receptors in both humans and rodents. Indeed, CB_1 receptor expression dissipates from white matter tracts to neuronal localization (13,14), where they have the ability to influence synaptic communication in addition to continuing to modulate several neuronal processes, including synaptogenesis and myelination (10,16,17). Consequently, early disruptions to the eCB system, such as by PCE, may have lifelong negative implications for brain development and behavioral health.

Indeed, recent research has linked PCE to several adverse birth and childhood outcomes, including lower birth weight, cardiovascular defects, lower brain volume, alterations in large-scale functional brain networks, and increased risk of neurobehavioral problems, such as attention-deficit/hyperactivity disorder (10,18–20). For example, one study found that PCE was associated with lower total gray and white matter volumes, as well as greater offspring psychopathology characteristics in 9- to 10-year-old children from the Adolescent Brain Cognitive Development (ABCD) Study cohort (21). In our recent study using the ABCD Study dataset, we found that children with PCE showed lower resting-state functional connectivity between large-scale attentional brain networks (i.e., salience network, ventral attention network) than that observed in unexposed youths (19). Other studies have demonstrated altered neurophysiological functioning, neurocognitive functioning (e.g., visuospatial working memory, response inhibition), and cortical thickness in adolescents and young adults with PCE (22–25), suggesting that effects of PCE may be evident even decades later, into adulthood.

While these studies reveal concerning alterations in whole-brain measures and large-scale neurocognitive network function following PCE, less is known about the impact on individual white matter pathways. White matter pathways have been implicated in varied neural processes and continue to develop across childhood and adolescence, with specific pathways maturing at different rates (26,27). Frontolimbic pathways, such as the fornix—which connects frontal regions with medial temporal and subcortical structures (e.g., hypothalamus)—show a high density of CB_1 receptors and are implicated in emotion- and memory-related processes and mood (26,28). As such, frontolimbic pathways may be particularly sensitive to early exposures, such as PCE.

Previous neuroimaging studies in both adolescents and adults suggest that frontolimbic pathways and regions are susceptible to cannabis exposure during other periods of substantial neurodevelopment, such as adolescence. For example, diffusion magnetic resonance imaging (dMRI) studies show that adults who reported early adolescent cannabis use demonstrated lower fractional anisotropy (FA) of frontolimbic pathways, such as superior and inferior longitudinal fasciculi and the uncinate fasciculus, than those with a later age of onset (29,30). FA, while low in specificity, may reflect a number of different changes in white matter, including myelination, axon density, axon diameter, or permeability (31). Nonetheless, current research suggests that frontolimbic pathways are sensitive to developmental cannabis and cannabinoid exposure. What remains unclear, however, is whether disruptions in frontolimbic development specifically due to cannabis use during pregnancy, are observable in childhood.

To address these gaps, the current study examined the impact of PCE on frontolimbic white matter microstructure in 9- to 10-year-old children from the ABCD Study. Based on previous research, we hypothesized that PCE would be associated with lower integrity of frontolimbic white matter pathways even when controlling for known confounders (e.g., prenatal alcohol, tobacco). In addition, while our main analyses focused on frontolimbic pathways, exploratory analyses examined the effects of PCE on nonfrontolimbic white matter pathways for completeness and to examine the specificity of results.

METHODS AND MATERIALS

Participants

For the current analysis, data were obtained from the ABCD Data Release 4.0 and included baseline cross-sectional data from 11,530 children from the ABCD Study (mean ± SD age = 118.99 ± 7.49 months; 47% female). Participants were included if they had available PCE (described below) and dMRI data. A manuscript-specific digital object identifier for this study is available at https://doi.org/10.15154/1523155. The parent or guardian (hereafter caregiver) of the participant provided informed consent, and the child gave assent to participate in this study. Local institutional review boards approved the study procedures at each site, and the centralized institutional review board was housed at the University of California, San Diego. More information about the ABCD Study is provided elsewhere (21).

PCE and Potential Covariates

PCE was determined by retrospective report (yes, no) from the caregiver. Caregivers reported on their child's race (non-White, White), biological sex, age at the time of the study, maternal education, and family income. Caregiver-reported tobacco, alcohol, and other substance use (e.g., cocaine) during pregnancy were collected for inclusion as covariates. Caregivers also reported on lifetime depression of the child's biological mother (binary covariate). These covariates were selected due to their known relationships with FA (32). Family identification and site identification were measured for use in statistical analyses as nested variables (family within site). Caregiver-reported youth prescription medication use, presence of an alcohol or other substance use problem in either parent, and youth-reported substance use (measured by ever trying alcohol, cocaine, cannabis, or other substances) were included as covariates in secondary analyses to determine robustness of results (see the Supplement).

Imaging Methods

The imaging protocol was standardized across the 21 ABCD Study data collection sites. MRI scanner (3T) platforms were used, including Siemens Prisma, General Electric 750, and Phillips. The harmonized imaging protocol includes resting-state, T1, T2, diffusion-weighted images and task-based

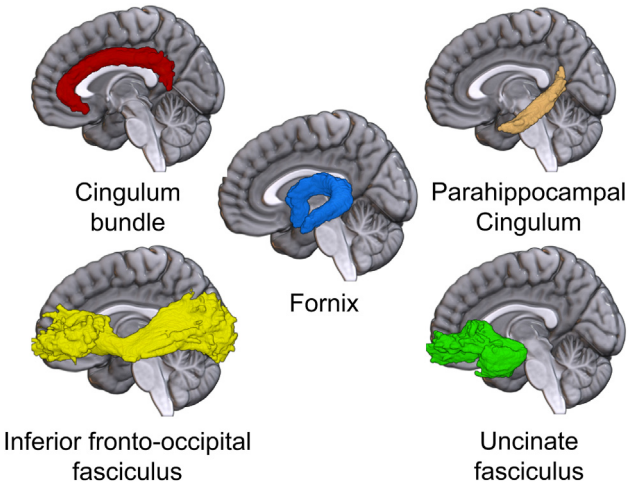

Figure 1. Frontolimbic white matter tracts of interest.

functional MRI (21). The dMRI image acquisition used a multiband echo planar imaging sequence with 96 diffusion directions and an acceleration factor of 3 (33). Centralized processing and analysis of MRI data was performed by the ABCD Data Analysis and Informatics Center. Brain microstructure using dMRI was analyzed, and head motion was estimated and corrected by quantifying an average frame-to-frame head movement. AtlasTrack was used to identify and label white matter tracts (33), and FA was computed for each tract in the right and left hemispheres separately. Primary analyses focused on the entire sample of participants. Secondary analyses included only (n = 10,114) participants with dMRI data that passed ABCD quality-control parameters (imgincl_dfmri_include = 1 and imgincl_t1w_include = 1) (see the Supplement).

Primary analyses utilized tabulated dMRI data from the National Institute of Mental Health Data Archive Data Release 4.0. We focused on FA of 10 (5 per hemisphere) frontolimbic white matter pathways: 1) the fornix, 2) cingulum bundle, 3) parahippocampal cingulum bundle, 4) uncinate fasciculus, and 5) inferior-fronto-occipital fasciculus (Figure 1). For completeness and to test for specificity of results to nonfrontolimbic pathways, we examined FA of the 21 nonfrontolimbic white matter tracts derived from AtlasTrack after adjusting for average FA of all tracts (whole brain) provided by AtlasTrack.

Statistical Analyses

First, we examined the frequency of children with versus without PCE. Next, linear mixed-effects models were used to test for correlations between PCE and sociodemographic factors, such as age and sex. Then, separate linear mixed-effects models were used to examine the impact of PCE (1 = exposed, 0 = unexposed) as a predictor of FA, with separate models conducted for the 10 separate tracts. False discovery rate (FDR) was used to correct for multiple comparisons (FDR-corrected $p < .05$). The following covariates were added to test for robustness of results: race/ethnicity; age; sex; maternal depression; parent education; family income; planned pregnancy; premature birth; and prenatal alcohol, tobacco, or other drug (e.g., cocaine) exposure. Random effects of family and site identity were also included. All analyses were performed in RStudio version 2022.12.0+353 using lme4 (34). We report upper and lower 95% CIs as well as p values. To test for robustness of results, we conducted several secondary analyses. First, we included additional covariates that may impact FA: youth prescription medical use, youth substance use, and presence of a parent drug or alcohol problem (see the Supplement). Second, we repeated analyses excluding one participant who had extreme values for FA (>0.9) across several tracts and one participant with an extreme FA value (>0.9) for the left fornix. Third, we repeated our analyses using the subset of participants (n = 10,114) who passed all ABCD quality-control parameters and excluded participants who were on any medications (n = 5365). Notably, the main results remained significant in these secondary analyses (see the Supplement).

For tracts that showed significant associations between FA and PCE, we explored whether these effects were driven by PCE before versus after maternal knowledge of pregnancy. These were modeled as separate factors given the overlap in use before and after knowledge of pregnancy, emulating recent PCE research (19,35). For tracts showing significant associations between FA and PCE, follow-up analyses explored the effects of PCE on transverse diffusivity, longitudinal diffusivity, and mean diffusivity (see the Supplement). Finally, to test for specificity of effects to frontolimbic pathways, we performed exploratory analyses examining the effects of PCE on FA of the 21 nonfrontolimbic pathways derived from AtlasTrack and whether main results remained significant while controlling for average FA of all tracts (frontolimbic and nonfrontolimbic). In addition, we provide exploratory associations between white matter and parent-reported neurobehavioral outcomes in the Supplement.

RESULTS

Prenatal Cannabis Exposure

In this sample, 6.04% of caregivers (n = 697) reported using cannabis during pregnancy. Demographics for the entire sample and separately by PCE groups are reported in Table 1. No significant difference in age or biological sex was observed between exposed and unexposed children. However, there were significant associations between PCE and various sociodemographic factors (see Table 1). Parents using cannabis reported learning of their pregnancy later, at 8.24 weeks on average, than those in the unexposed group (6.84 weeks, $p < .001$).

Effects of PCE on Frontolimbic White Matter Integrity Without Covariates

Compared with the unexposed group, children with PCE showed lower FA in the following 4 pathways: left fornix ($\beta = -0.004$, 95% CI, -0.006 to -0.00193, $p < .001$) (Figure 2A), right fornix ($\beta = -0.005$, 95% CI, -0.00665 to -0.00243, $p < .001$) (Figure 2B), right parahippocampal cingulum ($\beta = -0.004$, 95% CI, -0.00692 to -0.00110, $p = .007$) (Figure 2C), and left uncinate ($\beta = -0.003$, 95%

Table 1. Participant Demographics Overall and by PCE

Variable	Total, N = 11,530	PCE, n = 697	Unexposed, n = 10,833	Group Comparison
Age in Months, Mean (SD)	118.99 (7.49)	118.50 (7.66)	119.01 (7.49)	p = .06
Biological Sex, *n*				
Female	5507	347	5160	p = .15
Male	6203	350	5673	
Race/Ethnicity[a], *n*				
Non-White	5462	440	5022	$p < .001$[b]
White	6068	257	5811	
Week Learned of Their Pregnancy in Weeks, Mean (SD)	6.92 (6.78)	8.24 (7.25)	6.84 (6.74)	$p < .001$[b]
Parent Level of Education, *n*				
Less than high school	769	60	709	$p < .001$[b]
High school diploma/GED	1216	133	1083	
Some college	3382	311	3071	
Bachelor's degree	3258	111	3147	
Postgraduate degree	2888	82	2806	
Family Income[a], *n*				
Low income, <$50,000	3121	358	2763	$p < .001$[b]
Middle income, $50,000–$99,999	2981	168	2813	
High income, >$100,000	4441	108	4333	
Prenatal Alcohol Exposure, *n*				
Prenatal alcohol exposure	2845	418	2427	$p < .001$[b]
No prenatal alcohol exposure	8684	279	8405	
Prenatal Tobacco Exposure, *n*				
Prenatal tobacco exposure	1540	416	1124	$p < .001$[b]
No prenatal tobacco exposure	9988	281	9707	
Prenatal Exposure to Other Substances, *n*				
Prenatal substance exposure	114	65	49	$p < .001$[b]
No prenatal substance exposure	11,353	583	10,770	
Maternal Depression, *n*				
History of maternal depression	2569	282	2287	$p < .001$[b]
No history of maternal depression	8496	359	8137	
Premature Birth, *n*				
Premature birth	2155	110	2045	p = .2465
Not premature birth	9317	571	8746	
Planned Pregnancy, *n*				
Planned pregnancy	4365	501	3864	$p < .001$[b]
Unplanned pregnancy	7043	168	6875	

GED, general educational development; PCE, prenatal cannabis exposure.

[a]Values may not add up to total sample because of missing data or data not reported.

[b]$p < .001$.

CI, −0.00492 to −0.00024, p = .031) (Figure 2D). PCE was not associated with FA in the other frontolimbic tracts ($p > .05$).

Effects of PCE on Frontolimbic White Matter Integrity With Covariates and Multiple Comparisons Correction

After including covariates, the left fornix (β = −0.003, 95% CI, −0.00586 to −0.00202, p = .007), right fornix (β = −0.005, 95% CI, −0.00767 to −0.0000255, $p < .001$), right parahippocampal cingulum (β = −0.004, 95% CI, −0.00736 to −0.00026, p = .036), and left uncinate (β = −0.003, 95% CI, −0.00581 to −0.00013, p = .041) remained significantly negatively associated with PCE. However, only the right and left fornix survived FDR correction. Follow-up analyses showed that, for the right fornix, effects of PCE were significant before (β = −0.002, 95% CI, −0.00562 to −0.00026, p = .031) but not after (β = −0.012, 95% CI, −0.03328 to −0.00931, p = .27) knowledge of pregnancy. In contrast, the left fornix effects were significant for PCE after knowledge of pregnancy (β = −0.02567, 95% CI= −0.04620 to −0.00514, p = .014) and not significant for before knowledge (β = −0.00221, 95% CI= −0.00479 to −0.00037, p = .094). After adjusting for covariates, the effects of PCE on the right and left fornix FA were r = −0.04 and r = −0.029, respectively. The right

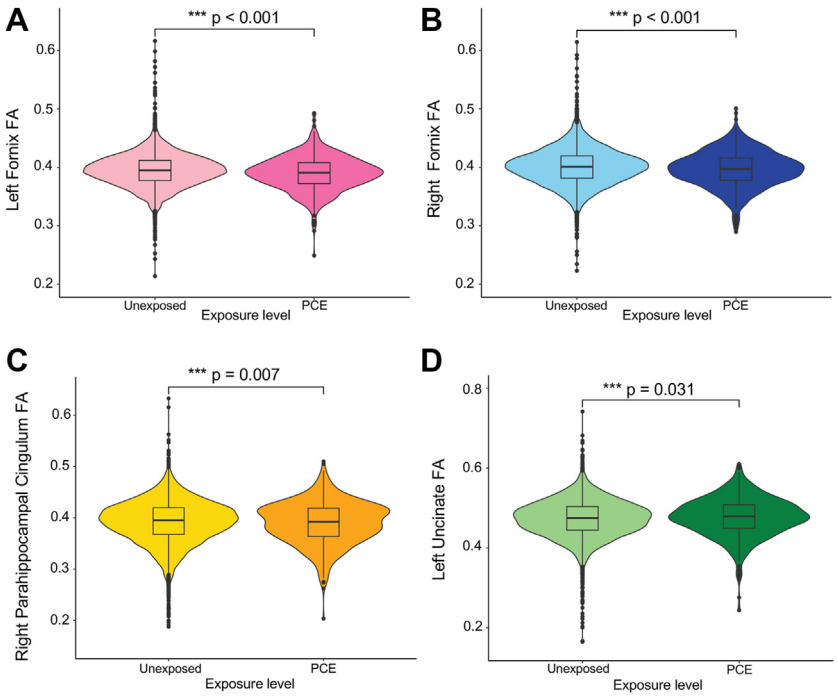

Figure 2. Impact of prenatal cannabis exposure (PCE) on fractional anisotropy (FA) of the **(A)** left fornix, **(B)** right fornix, **(C)** right parahippocampal cingulum, and **(D)** left uncinate. All results remained significant after adjusting for covariates. Only the left and right fornix remained significant after adjusting for multiple comparisons. Error bars represent standard error. *$p < .05$. Means shown are not adjusted for covariates. Two outliers with extreme values on FA were excluded.

parahippocampal cingulum, right uncinate, and left uncinate did not have specific effects before or after knowledge (*p*s > .05) of pregnancy.

Effects on Nonfrontolimbic Pathways

To test whether results were specific to frontolimbic pathways, we explored effects of PCE on the 21 other white matter pathways included in AtlasTrack. After adjusting for covariates, 4 of the 21 tracts were significantly negatively associated with PCE: the left inferior frontal superior frontal cortex (IFSFC, frontal aslant tract), the right IFSFC, the left superior longitudinal fasciculus, and the right superior longitudinal fasciculus (see the Supplement). However, only the left and right IFSFC survived FDR correction. In addition, the effects of PCE on FA of the right fornix remained significant when adjusting for FA of all diffusion tensor imaging tract fibers (see the Supplement).

DISCUSSION

In this study, we examined the impact of PCE on the integrity of frontolimbic white matter tracts in a large sample of 9- to 10-year-old children from the ABCD Study. We found that PCE was associated with lower FA of the left fornix, right fornix, right parahippocampal cingulum, and left uncinate. After quality control, adjusting for covariates, and multiple comparisons correction, the association between PCE and reduced FA remained significant only in the right and left fornix. Given the critical role of frontolimbic pathways in emotion, memory, and mood (36–38), our findings suggest that PCE has observable associations with neurodevelopment a decade following exposure. These findings may be in accordance with the double hit hypothesis, wherein PCE represents the first insult or vulnerability to the eCB system, and a "second hit" or postnatal stressor later in life (i.e., psychosocial stress, environmental stressors) may be needed to reveal neurobehavioral effects of PCE (39,40). Thus, altered microstructure of frontolimbic pathways may contribute to the reported elevated risk of cognitive, behavioral, and social problems reported in youths with PCE (35). Notably, the observed effects of PCE on fornix FA were small, yet reliable. Future studies are needed to understand the impacts of small changes in brain structure or function on neurodevelopment and neuropsychiatric risk.

PCE was associated with lower FA of the fornix, which connects the frontal lobe to the limbic system and is involved in emotion regulation, cognition, and episodic memory recall (41). In children and adolescents, lower FA of the fornix has previously been linked to attention-deficit/hyperactivity disorder, poorer cognitive functioning, and greater externalizing symptoms (35,42,43). Results of the current study suggest that altered frontolimbic white matter pathways may underlie the reported link between PCE and memory, learning, and attention deficits (35,44). Longitudinal associations among PCE, white matter microstructure, and cognitive and behavioral outcomes should be explored in future waves of the ABCD Study.

Interestingly, in our follow-up analyses, we found that the effects of PCE on right fornix FA were specific to PCE before knowledge of pregnancy, whereas effects on the left fornix were specific to PCE after knowledge of pregnancy. The left fornix is thought to carry verbal memory information, and the right fornix is thought to carry visuospatial memory information; therefore, the observed laterality effect may reflect a differential sensitivity of verbal memory, visuospatial memory, and emotion-related processing to PCE that is experienced

earlier versus later in gestation, respectively (45). This hypothesis requires further study.

In this sample, caregivers in the PCE group reported finding out that they were pregnant at over 8 weeks, on average, which is after the fetal eCB system is thought to be intact and functional—at around 5 weeks gestation (10). Given the critical role of the eCB system in fetal as well as placental homeostasis, synaptogenesis, and myelination (10,16,17,41,46), it is possible that early gestational exposure can affect the developing eCB system and may have implications for neurodevelopment. Our findings are noteworthy because the fornix is one of the earliest white matter tracts to develop and can be detected in the fetal brain as early as 13 weeks into gestation (44,47,48). By 18 to 20 weeks into gestation, the fornix begins to resemble its adult-like structure (47,49,50). This is especially relevant given the dense expression of CB_1 receptors in developing white matter tracts (14). The observed null effects of PCE on other frontolimbic pathways may be due to their later developmental appearance; for example, the inferior fronto-occipital fasciculus appears at around 20 weeks of gestation (47).

Notably, our exploratory analyses indicated that only 2 of the tested 21 nonfrontolimbic pathways (i.e., left and right IFSFC) were associated with PCE after adjusting for covariates and multiple comparisons. This suggests that the previously observed effects of PCE on total white matter volume (35) may be driven by specific pathways and that certain white matter pathways may be more sensitive to the effects of PCE than others. Our analyses suggest that the fornix and the IFSFC may be particularly sensitive to PCE and that these effects are not limited to frontolimbic pathways. The IFSFC is a recently discovered association fiber tract that connects the inferior frontal cortex and superior frontal cortex. While the functional role of the IFSFC remains unclear, a recent systematic review implicates this tract in various functions, including speech and language, working memory, visual-motor activities, and attention (51). Therefore, observed effects of PCE on FA of the IFSFC may contribute to previously reported cognitive alterations in children with PCE (52). Future studies should explore longitudinal associations between white matter integrity and neurobehavioral outcomes, especially as the ABCD Study sample enters adolescence. For instance, rodent studies have found that PCE is associated with deficits in social behavior (53); thus, future preclinical work should investigate the role of alterations in white matter integrity as a contributor to these behavioral effects.

Examining the effects of PCE in a large cohort such as the ABCD Study afforded an ability to detect more precise and reliable effects (54) of PCE on white matter microstructure. Large samples also provide enhanced statistical power to detect small effect sizes of statistical significance, which may limit the real-world relevance of the findings. However, Carey *et al.* noted that even effects that are perceived as small can have large impacts when scaled to large populations (55). Furthermore, prenatal exposure to substances, such as alcohol, are associated with similar small effect sizes on white matter integrity, ranging from $\beta = -0.01$ to -0.03 (our values highlight even smaller effects, ranging from -0.003 to -0.006) (56). However, due to pervasive underreporting of substance use, particularly during pregnancy (57), these estimates may underestimate effects of PCE. Furthermore, a recent multimethod survey of effect sizes within the ABCD Study revealed that effect sizes are much smaller in large, real-world samples (median $r = 0.03$) than commonly used heuristics established by Cohen (e.g., small effect: $r = 0.1$), which are likely miscalibrated to effects typically found in psychological research (58). The article by Owens *et al.* proposed new benchmarks for the ABCD Study; according to these new benchmarks, the observed effects of PCE on fornix FA would approximate the median effect size observed (semipartial rs = 0.028–0.04). For a comparison, Owens *et al.* suggested that even highly intuitive effects, such as the effects of physical activity on weight, also fall within this effect size range ($r = 0.03$), suggesting that intuition tends to overestimate effect sizes (58). It is also possible that such small effects can accumulate over time and that larger effects of PCE on neurobehavioral outcomes will emerge longitudinally (58,59). Nonetheless, we observed—according to Cohen's heuristic—small yet reliable effects of PCE on frontolimbic white matter microstructure in children. Future studies are needed to comprehensively understand the impacts of changes in brain structure or function on neurodevelopment and neuropsychiatric risk.

Strengths of this study include the large sample size ($n >$ 10,000) and the fact that the results were robust to several different approaches and covariate adjustment, such as prenatal exposure to alcohol and tobacco, maternal depression, total brain FA, and MRI image quality. However, several limitations of this study should be noted. PCE was assessed using retrospective caregiver report from nearly a decade ago, which is highly susceptible to reporting bias, and there is a strong likelihood of underreported cannabis usage rates during pregnancy. Not surprisingly, self-reports of cannabis use during pregnancy are known to underestimate toxicology reports (60). Therefore, the observed neurodevelopmental effects may underestimate the effects of PCE. Although several steps were taken to minimize between-site and between-scan platform differences by the ABCD Study team and in our analyses, different MR scanners and manufacturers may still influence results (21). Future studies should incorporate more objective measures, such as regular drug testing during gestation or the collection of maternal and cord blood. In addition, in-depth data were not collected on cannabis use, including potency or route of administration. Subsequent research should explore these use patterns and effects on offspring in greater detail.

Conclusions

In summary, rapidly increasing access to and higher potency of cannabis raises concerns about neurodevelopmental effects on vulnerable populations, such as children. Our results may contribute to recent findings of neurobehavioral alterations in children with PCE to include variation in frontolimbic white matter development, particularly in the fornix, a pathway that is critical for emotional learning and memory. Future studies are needed to increase our understanding of the impacts of changes in brain structure or function on neurodevelopment and risk of neurobehavioral problems.

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A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/. This manuscript reflects the views of the authors and may not reflect the opinions or views of the National Institutes of Health or ABCD consortium investigators.

The ABCD data repository grows and changes over time. The ABCD data used in this report came from https://doi.org/10.15154/1523041.

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JME and HAM conceptualized and designed the project. JME, HAM, and CGZ analyzed and interpreted the data. All authors critically revised the final version of the manuscript. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report.

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REFERENCES

1. Substance Abuse and Mental Health Services Administration (2022): Marijuana and pregnancy. Available at: https://www.samhsa.gov/marijuana/marijuana-pregnancy. Accessed August 1, 2023.
2. Brown QL, Sarvet AL, Shmulewitz D, Martins SS, Wall MM, Hasin DS (2017): Trends in marijuana use among pregnant and nonpregnant reproductive-aged women, 2002–2014. JAMA 317:207–209.
3. Chang JC, Tarr JA, Holland CL, De Genna NM, Richardson GA, Rodriguez KL, *et al.* (2019): Beliefs and attitudes regarding prenatal marijuana use: Perspectives of pregnant women who report use. Drug Alcohol Depend 196:14–20.
4. Young-Wolff KC, Sarovar V, Tucker LY, Avalos LA, Alexeeff S, Conway A, *et al.* (2019): Trends in marijuana use among pregnant women with and without nausea and vomiting in pregnancy, 2009–2016. Drug Alcohol Depend 196:66–70.
5. Volkow ND, Han B, Compton WM, McCance-Katz EF (2019): Self-reported medical and nonmedical cannabis use among pregnant women in the United States. JAMA 322:167–169.
6. Branum AM, Ahrens KA (2017): Trends in timing of pregnancy awareness among US women. Matern Child Health J 21:715–726.
7. Levy NS, Mauro PM, Mauro CM, Segura LE, Martins SS (2021): Joint perceptions of the risk and availability of cannabis in the United States, 2002–2018. Drug Alcohol Depend 226:108873.
8. ElSohly MA, Chandra S, Radwan M, Majumdar CG, Church JC (2021): A comprehensive review of cannabis potency in the United States in the last decade. Biol Psychiatry Cogn Neurosci Neuroimaging 6:603–606.
9. Baglot SL, VanRyzin JW, Marquardt AE, Aukema RJ, Petrie GN, Hume C, *et al.* (2022): Maternal-fetal transmission of delta-9-tetrahydrocannabinol (THC) and its metabolites following inhalation and injection exposure during pregnancy in rats. J Neurosci Res 100:713–730.
10. Wu CS, Jew CP, Lu HC (2011): Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. Future Neurol 6:459–480.
11. Berghuis P, Rajnicek AM, Morozov YM, Ross RA, Mulder J, Urbán GM, *et al.* (2007): Hardwiring the brain: Endocannabinoids shape neuronal connectivity. Science 316:1212–1216.
12. Mulder J, Aguado T, Keimpema E, Barabás K, Rosado CJB, Nguyen L, *et al.* (2008): Endocannabinoid signaling controls pyramidal cell specification and long-range axon patterning. Proc Natl Acad Sci USA 105:8760–8765.
13. Romero J, Garcia-Palomero E, Berrendero F, Garcia-Gil L, Hernandez ML, Ramos JA, Fernández-Ruiz JJ (1997): Atypical location of cannabinoid receptors in white matter areas during rat brain development. Synapse 26:317–323.
14. Mato S, Del Olmo E, Pazos A (2003): Ontogenetic development of cannabinoid receptor expression and signal transduction functionality in the human brain. Eur J Neurosci 17:1747–1754.
15. Díaz-Alonso J, Guzmán M, Galve-Roperh I (2012): Endocannabinoids via CB_1 receptors act as neurogenic niche cues during cortical development. Philos Trans R Soc B Biol Sci 367:3229–3241.
16. Anavi-Goffer S, Mulder J (2009): The polarised life of the endocannabinoid system in CNS development. Chembiochem 10:1591–1598.
17. Huizink AC, Mulder EJH (2006): Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. Neurosci Biobehav Rev 30:24–41.
18. Thompson R, DeJong K, Lo J (2019): Marijuana use in pregnancy: A review. Obstet Gynecol Surv 74:415–428.
19. Faraj MM, Evanski J, Zundel CG, Peters C, Brummelte S, Lundahl L, Marusak HA (2023): Impact of prenatal cannabis exposure on functional connectivity of the salience network in children. J Neurosci Res 101:162–171.
20. Marchand G, Masoud AT, Govindan M, Ware K, King A, Ruther S, *et al.* (2022): Birth outcomes of neonates exposed to marijuana in utero: A systematic review and meta-analysis. JAMA Netw Open 5:e2145653.
21. Casey BJ, Cannonier T, Conley MI, Cohen AO, Barch DM, Heitzeg MM, *et al.* (2018): The adolescent brain cognitive development (ABCD) study: Imaging acquisition across 21 sites. Dev Cogn Neurosci 32:43–54.
22. El Marroun H, Tiemeier H, Franken IHA, Jaddoe VWV, van der Lugt A, Verhulst FC, *et al.* (2016): Prenatal cannabis and tobacco exposure in relation to brain morphology: A prospective neuroimaging study in young children. Biol Psychiatry 79:971–979.
23. Smith AM, Mioduszewski O, Hatchard T, Byron-Alhas san A, Fall C, Fried PA (2016): Prenatal marijuana exposure impacts executive functioning into young adulthood: An fMRI study. Neurotoxicol Teratol 58:53–59.
24. Smith AM, Fried PA, Hogan MJ, Cameron I (2006): Effects of prenatal marijuana on visuospatial working memory: An fMRI study in young adults. Neurotoxicol Teratol 28:286–295.
25. Smith AM, Fried PA, Hogan MJ, Cameron I (2004): Effects of prenatal marijuana on response inhibition: An fMRI study of young adults. Neurotoxicol Teratol 26:533–542.
26. Lebel C, Treit S, Beaulieu C (2019): A review of diffusion MRI of typical white matter development from early childhood to young adulthood. NMR Biomed 32:e3778.

27. Toga AW, Thompson PM, Sowell ER (2006): Mapping brain maturation. Trends Neurosci 29:148–159.
28. Shollenbarger SG, Price J, Wieser J, Lisdahl K (2015): Poorer fronto-limbic white matter integrity is associated with chronic cannabis use, FAAH genotype, and increased depressive and apathy symptoms in adolescents and young adults. Neuroimage Clin 8:117–125.
29. Cousijn J, Toenders YJ, van Velzen LS, Kaag AM (2022): The relation between cannabis use, dependence severity and white matter microstructure: A diffusion tensor imaging study. Addict Biol 27:e13081.
30. Orr JM, Paschall CJ, Banich MT (2016): Recreational marijuana use impacts white matter integrity and subcortical (but not cortical) morphometry. NeuroImage Clin 12:47–56.
31. Meinert S, Repple J, Nenadic I, Krug A, Jansen A, Grotegerd D, *et al.* (2019): Reduced fractional anisotropy in depressed patients due to childhood maltreatment rather than diagnosis. Neuropsychopharmacology 44:2065–2072.
32. Dick AS, Lopez DA, Watts AL, Heeringa S, Reuter C, Bartsch H, *et al.* (2021): Meaningful associations in the adolescent brain cognitive development study. Neuroimage 239:118262.
33. Hagler DJ, Hatton SN, Cornejo MD, Makowski C, Fair DA, Dick AS, *et al.* (2019): Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. Neuroimage 202:116091.
34. Bates D, Mächler M, Bolker BM, Walker SC (2015): Fitting linear mixed-effects models using lme4. J Stat Soft 67:1–48.
35. Paul SE, Hatoum AS, Fine JD, Johnson EC, Hansen I, Karcher NR, *et al.* (2021): Associations between prenatal cannabis exposure and childhood outcomes: Results from the ABCD study. JAMA Psychiatry 78:64–76.
36. Perez DL, Vago DR, Pan H, Root J, Tuescher O, Fuchs BH, *et al.* (2016): Frontolimbic neural circuit changes in emotional processing and inhibitory control associated with clinical improvement following transference-focused psychotherapy in borderline personality disorder. Psychiatry Clin Neurosci 70:51–61.
37. Herringa RJ (2017): Trauma, PTSD, and the developing brain. Curr Psychiatry Rep 19:69.
38. Hermens DF, Jamieson D, Fitzpatrick L, Sacks DD, Iorfino F, Crouse JJ, *et al.* (2022): Sex differences in fronto-limbic white matter tracts in youth with mood disorders. Psychiatry Clin Neurosci 76:481–489.
39. Richardson KA, Hester AK, McLemore GL (2016): Prenatal cannabis exposure – The "first hit" to the endocannabinoid system. Neurotoxicol Teratol 58:5–14.
40. Calcia MA, Bonsall DR, Bloomfield PS, Selvaraj S, Barichello T, Howes OD (2016): Stress and neuroinflammation: A systematic review of the effects of stress on microglia and the implications for mental illness. Psychopharmacol (Berl) 233:1637–1650.
41. Kozakiewicz ML, Grotegut CA, Howlett AC (2021): Endocannabinoid system in pregnancy maintenance and labor: A mini-review. Front Endocrinol (Lausanne) 12:699951.
42. Cioffredi LA, Anderson H, Loso H, East J, Nguyen P, Garavan H, Potter A (2022): Prenatal cannabis exposure predicts attention problems, without changes on fMRI in adolescents. Neurotoxicol Teratol 91:107089.
43. Brenner RG, Smyser CD, Lean RE, Kenley JK, Smyser TA, Cyr PEP, *et al.* (2021): Microstructure of the dorsal anterior cingulum bundle in very preterm neonates predicts the preterm behavioral phenotype at 5 years of age. Biol Psychiatry 89:433–442.
44. Nashed MG, Hardy DB, Laviolette SR (2020): Prenatal cannabinoid exposure: Emerging evidence of physiological and neuropsychiatric abnormalities. Front Psychiatry 11:624275.
45. Costanzi M, Cianfanelli B, Saraulli D, Lasaponara S, Doricchi F, Cestari V, Rossi-Arnaud C (2019): The effect of emotional valence and arousal on Visuo-spatial working memory: Incidental emotional learning and memory for object-location. Front Psychol 10:2587.
46. Fonseca BM, Correia-Da-Silva G, Almada M, Costa MA, Teixeira NA (2013): The endocannabinoid system in the postimplantation period: A role during decidualization and placentation. Int J Endocrinol 2013:510540.
47. Horgos B, Mecea M, Boer A, Szabo B, Buruiana A, Stamatian F, *et al.* (2020): White matter dissection of the fetal brain. Front Neuroanat 14:584266.
48. Cullen KR, Klimes-Dougan B, Muetzel R, Mueller BA, Camchong J, Houri A, *et al.* (2010): Altered white matter microstructure in adolescents with major depression: A preliminary study. J Am Acad Child Adolesc Psychiatry 49:173–183.e1.
49. Gindes L, Weissmann-Brenner A, Weisz B, Zajicek M, Geffen KT, Achiron R (2011): Identification of the fetal hippocampus and fornix and role of 3-dimensional sonography. J Ultrasound Med 30:1613–1618.
50. Ge X, Shi Y, Li J, Zhang Z, Lin X, Zhan J, *et al.* (2015): Development of the human fetal hippocampal formation during early second trimester. Neuroimage 119:33–43.
51. La Corte E, Eldahaby D, Greco E, Aquino D, Bertolini G, Levi V, *et al.* (2021): The frontal aslant tract: A systematic review for neurosurgical applications. Front Neurol 12:641586.
52. Hiraoka D, Makita K, Hamatani S, Tomoda A, Mizuno Y (2023): Effects of prenatal cannabis exposure on developmental trajectory of cognitive ability and brain volumes in the adolescent brain cognitive development (ABCD) study. Dev Cogn Neurosci 60:101209.
53. Weimar HV, Wright HR, Warrick CR, Brown AM, Lugo JM, Freels TG, McLaughlin RJ (2020): Long-term effects of maternal cannabis vapor exposure on emotional reactivity, social behavior, and behavioral flexibility in offspring. Neuropharmacology 179:108288.
54. Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, *et al.* (2022): Reproducible brain-wide association studies require thousands of individuals. Nature 603:654–660.
55. Carey EG, Ridler I, Ford TJ, Stringaris A (2023): Editorial Perspective: When is a 'small effect' actually large and impactful? J Child Psychol Psychiatry 1–5.
56. Long X, Lebel C (2022): Evaluation of brain alterations and behavior in children with low levels of prenatal alcohol exposure. JAMA Netw Open 5:e225972.
57. Garg M, Garrison L, Leeman L, Hamidovic A, Borrego M, Rayburn WF, Bakhireva L (2016): Validity of self-reported drug use information among pregnant women. Matern Child Health J 20:41–47.
58. Owens MM, Potter A, Hyatt CS, Albaugh M, Thompson WK, Jernigan T, *et al.* (2021): Recalibrating expectations about effect size: A multi-method survey of effect sizes in the ABCD study. PLoS One 16:1–13.
59. Kwong ASF (2019): Examining the longitudinal nature of depressive symptoms in the avon longitudinal study of parents and children (ALSPAC). Wellcome Open Res 4:126.
60. Young-Wolff KC, Sarovar V, Tucker LY, Goler N, Conway A, Weisner C, *et al.* (2020): Validity of self-reported cannabis use among pregnant females in northern California. J Addict Med 14:287–292.