Commentary

Biological Psychiatry: GOS

Evaluating Evidence Supporting an Effect of Prenatal Cannabis Exposure on White Matter Integrity

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Accumulating evidence suggests that prenatal cannabis exposure may be associated with a small increase in adverse outcomes (e.g., preterm birth, low birth weight, psychopathology) (1,2). However, use during pregnancy continues to rise (~100% increase in the past 2 decades) (3) and the putative mechanisms through which these associations may arise remain poorly understood and rarely studied (4). In the largest study to date of white matter structure and prenatal cannabis exposure, presented in the current issue of *Biological Psychiatry: Global Open Science*, Evanski *et al.* (5) show that prenatal cannabis exposure is associated with reduced fractional anisotropy (FA) of the left and right fornix. These findings provide important clues to mechanisms through which prenatal cannabis exposure may influence behavioral outcomes and highlight contemporary challenges currently confronting the study of complex behavior and biology, as well as prenatal cannabis exposure.

Using the baseline wave (ages 9–10) of the longitudinal Adolescent Brain Cognitive Development (ABCD) Study (N = 11,530; n = 697 with prenatal cannabis exposure), Evanski *et al.* (5) tested whether prenatal cannabis exposure is associated with FA of 5 a priori frontolimbic white matter tracts. The selection of these tracts is motivated primarily by: 1) prior observations in cannabis users that frontolimbic tracts are among the tracts that are more sensitive to an earlier age of onset, and 2) the hypothesis that cannabinoid type 1 receptors, which are highly expressed along several white matter tracts, including frontolimbic tracts, will mediate the effects of prenatal cannabis exposure on the brain. Alternative mechanisms of action, such as reduced placental neuroinflammation (6), might then be expected to yield associations in other regions. Post hoc analyses were conducted across all white matter tracts; however, it is unclear whether those findings survive correction with additional necessary covariates (i.e., substance use initiation, family history of drug problems, and limited to scans that pass quality control). Analyses focused on one white matter measure (FA) that can be derived from diffusion-weighted imaging scans. Three more measures (transverse, longitudinal, and mean diffusivity) were examined in post hoc analyses, but these analyses were limited to the 3 regions most significant in analyses of FA. While FA is widely used in the literature, there is no guarantee that it is the diffusion weighted imaging measure that will be most sensitive to the effects of prenatal cannabis exposure.

After correction for covariates and multiple comparisons, associations of prenatal cannabis exposure with reduced FA of the left and right fornix remained significant. While the effect of prenatal cannabis on FA observed by Evanski *et al.* (5) is quite small (semipartial rs = 0.028–0.04), this range of effects is consistent with prior mass-univariate imaging studies with very large samples (i.e., brain-wide association studies) (7). In particular, it is not that surprising that the observable correlation between a prenatal exposure and the adolescent brain would be small, as the brain has had around a decade to adapt.

The ABCD Study provides some data on the timing of prenatal exposures, most notably whether exposure occurred before and/or after the mother learned she was pregnant (on average, mothers learned they were pregnant at 6.9 weeks gestation). Post hoc analyses examining the effects of the timing of cannabis exposure found that associations in the right fornix were driven by prenatal cannabis exposure before knowledge of pregnancy, while associations in the left fornix were driven by exposure after knowledge of pregnancy. However, it remains unclear whether the 2 groups differ and thus whether the effects are truly specific to the timing of exposure.

Supplemental analyses adjusted for additional covariates, including youth substance use and family history of drug or alcohol problems. These found that associations with the fornix were attenuated, leading to a null association in the left fornix and a nominally significant association in the right fornix. The ABCD Study's family history measures also do not include an item specific to family history of problems with cannabis use. As such, previous studies have included supplemental analyses controlling for a polygenic score of cannabis use disorder risk (1,2), an approach that was not adopted by Evanski *et al.* (5). Notably, a polygenic score for cannabis use disorder risk has previously been found to be associated with reduced total white matter volume in this sample (8). It was also not evaluated whether associations are independent of pregnancy risk variables that are correlated with prenatal cannabis exposure (e.g., use of prenatal vitamins, mother's age at birth) (2). Thus, these results suggest that the association of prenatal cannabis exposure with lower white matter tract integrity may not be entirely independent of correlated risk factors, including family history and genetic risk for substance use, substance use initiation, and pregnancy-related risk factors.

It is speculated that altered microstructure of frontolimbic tracts may contribute to the adverse outcomes associated with prenatal cannabis exposure, including associations with

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psychopathology and cognition previously observed in this sample (1,2). However, post hoc analyses tested the association of FA in the left and right fornix with measures of childhood psychopathology and cognition, finding no significant associations. This observation challenges the interpretation that these magnetic resonance imaging–derived measures could represent mechanisms through which prenatal cannabis exposure induces variability in behavior. Indeed, these effects could be fully independent of any observed behavioral consequences, or they may reflect the influence of risk factors that are correlated with prenatal cannabis exposure.

Other limitations stem from the design of the ABCD Study. Most notably, participants were enrolled as adolescents. As such, all measures of prenatal exposure are based on retrospective recall and may suffer from underreporting, and there are no biological measures of prenatal exposure or the prenatal environment. Further, data on the mother's use before and after pregnancy are not available, nor are data on the method of delivery (e.g., blunt, edible, vaping, oil), strength or strain of cannabis used, or the timing and frequency of use during pregnancy. In addition, while there is increasing recognition that paternal substance use preconception may also influence offspring outcomes (4), no data on paternal use were collected.

These limitations point to exciting directions for future research. Studies that begin enrollment around pregnancy are needed to evaluate when effects of prenatal exposures first emerge and whether other environmental factors may offer any protective effects. New large, nationwide studies such as the Healthy Brain and Child Development Study (9), which enrolls participants during pregnancy, will also provide opportunities to evaluate the influence of the prenatal environment on development with improved measurement of exposures. However, the limitations of the current study also point to the need for targeted datasets designed to test specific hypotheses surrounding early life exposures, with fewer of the trade-offs that come with the wide and shallow phenotyping that has become emblematic of the big-data approach to mental health research.

Overall, this is a timely and rigorous study that significantly advances our understanding of the effects of prenatal cannabis exposure on the brain. The strengths of the study are numerous, including the large sample size and the racial, ethnic, economic, and geographic diversity of the sample. While the results point to an effect of prenatal cannabis exposure on the brain's white matter, the question of whether effects on the brain explain the adverse mental health and cognitive outcomes associated with prenatal cannabis exposure remains unanswered. Further research with deeper phenotyping of prenatal exposures is needed to evaluate whether associations of prenatal cannabis with brain metrics is independent of its correlated risk factors. Until such a time, caution surrounding the use of cannabis during pregnancy is likely warranted.

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