Archival Report

Biological Psychiatry

Prenatal Cannabis and Tobacco Exposure in Relation to Brain Morphology: A Prospective Neuroimaging Study in Young Children

Hanan El Marroun, Henning Tiemeier, Ingmar H.A. Franken, Vincent W.V. Jaddoe, Aad van der Lugt, Frank C. Verhulst, Benjamin B. Lahey, and Tonya White

ABSTRACT

BACKGROUND: Cannabis use during pregnancy has been associated with negative behavioral outcomes and psychopathology in offspring. However, there has been little research evaluating alterations in brain structure as a result of maternal cannabis use. In this prospective study, we investigated the association between prenatal cannabis exposure and brain morphology in young children.

METHODS: We matched 96 children prenatally exposed to tobacco only (without cannabis) with 113 unexposed control subjects on the basis of age and gender and subsequently selected 54 children exposed to prenatal cannabis (mostly combined with tobacco exposure). These children (aged 6 to 8 years) were part of a population-based study in the Netherlands, the Generation R Study, and were followed from pregnancy onward. We assessed brain volumetric measures and cortical thickness in magnetic resonance imaging scans using FreeSurfer. We performed vertexwise analyses in FreeSurfer and linear regression analyses adjusting for relevant covariates using Statistical Package for the Social Sciences.

RESULTS: Prenatal cannabis exposure was not associated with global brain volumes, such as total brain volume, gray matter volume, or white matter volume. However, prenatal cannabis exposure was associated with differences in cortical thickness: compared with nonexposed control subjects, cannabis-exposed children had thicker frontal cortices. Prenatal tobacco exposure compared with nonexposed control subjects was associated with cortical thinning, primarily in the superior frontal and superior parietal cortices.

CONCLUSIONS: Our findings suggest an association between prenatal cannabis exposure and cortical thickness in children. Further research is needed to explore the causal nature of this association.

Keywords: Brain morphology, Neuroimaging, Pediatric brain development, Population-based study, Prenatal cannabis exposure, Prenatal tobacco exposure

http://dx.doi.org/10.1016/j.biopsych.2015.08.024

Worldwide, cannabis is commonly used among pregnant women with prevalence varying from 2% to 13% (1–4). Prenatal cannabis use is an important issue, as it may have consequences on health and brain development in offspring (5,6).

The long-term consequences of prenatal cannabis exposure on neurodevelopment have been largely investigated in two longitudinal studies. In 1978, the Ottawa Prenatal Prospective Study (OPPS) collected behavioral data from offspring of a middle-class population of pregnant women who smoked cannabis (7). In 1982, the Maternal Health Practices and Child Development project investigated the long-term behavioral consequences of prenatal cannabis exposure in a low-income African-American population (8). Results from these cohorts suggest that prenatal cannabis exposure has both short- and long-term consequences. For example, prenatal cannabis has been associated with aberrant behavior in newborns (9), cognitive deficits, impairments in inhibitory control, delinquency, and increased risk of drug abuse later in life (10–15). In the Generation R Study, a population-based prospective cohort in the Netherlands, which started in 2002, our group assessed the associations between prenatal cannabis and several offspring outcomes. This recent cohort is important, because improved breeding technology has significantly increased Δ^9-tetrahydrocannabinol (THC) levels in marijuana and hashish (16). Data from the Generation R cohort have shown growth retardation and decreased blood flow in the fetus (17,18) and attention and aggression problems in childhood (19) associated with prenatal cannabis exposure.

While the above-mentioned studies suggest that prenatal cannabis exposure may be harmful for the developing fetus, there is still little information as to the extent such early cannabis exposure can have persistent effects on brain development. To our knowledge, no information is available concerning the potential consequences of prenatal cannabis exposure on brain morphological differences later in life.

ISSN: 0006-3223

In a functional magnetic resonance imaging (fMRI) study, the OPPS demonstrated that young adults prenatally exposed to cannabis have increased activation in several brain regions during a visuospatial working memory task (left inferior and middle frontal gyri, left parahippocampal gyrus, left middle occipital gyrus, and left cerebellum). During this task, decreased activation was observed in right inferior and middle frontal gyri, suggesting that prenatal marijuana alters neural function during visuospatial working memory processing (20). Additionally, during a response inhibition task, increased activation was observed in the bilateral prefrontal cortex and right premotor cortex and decreased activation was observed in the left cerebellum (21), proposing that prenatal cannabis exposure is associated with neural activation during response inhibition. However, it was unclear whether these differences in activation were the result of differences in brain morphology, as this was not assessed in these fMRI studies (20,21). Moreover, these fMRI studies have some limitations, including a small sample size, confounding by current cannabis use, and challenges relating to the reliability of fMRI.

The current structural MRI study is focused on preadolescent children aged 6 to 8 years, an age range before the risk period of cannabis use in children. Pregnant mothers who smoke cannabis also tend to smoke tobacco. To disentangle the associations of smoking cannabis and tobacco with brain morphology, it is important to take into account tobacco smoking during pregnancy. Prenatal tobacco exposure has been associated with thinner orbitofrontal, middle frontal, and parahippocampal cortices, particularly in girls (22,23). Previously, we demonstrated that prenatal tobacco smoking was associated with thinner cortices in children aged 6 to 8 years (24). We used this study as a starting point to investigate the association of prenatal exposure to cannabis with brain morphology in 6- to 8-year-old children. Our hypothesis is that prenatal cannabis exposure will be associated with global morphological differences in the offspring brain, similar or even increased as compared with the association between prenatal tobacco exposure and brain morphology.

METHODS AND MATERIALS

Design and Setting

Subjects were recruited from an ongoing population-based prospective cohort, the Generation R Study. The study design has been described previously (25) and was approved by the Medical Ethics Committee (MEC) of the Erasmus Medical Centre. Written informed consent was obtained from all participants and the MEC requested to preinform the participants about the purpose of this MRI study (MEC 2008-140). In September 2009, 6- to 8-year-old children from the Generation R Study were invited to participate in an MRI component (26). Approximately 20% of the families declined to participate in this component. Exclusion criteria were having a significant motor or sensory disorder, moderate to severe head trauma with loss of consciousness, neurological disorders (including seizure disorder, neuromotor disorder, or a history of brain tumors), claustrophobia, and contraindications to MRI (e.g., having a pacemaker).

We selected all children exposed prenatally to cannabis (mostly combined with tobacco) with structural MRI data (n = 54) and children prenatally exposed to only tobacco (without cannabis) (n = 97). The unexposed control subjects (n = 113) were matched based on age and gender using a fuzzy matching procedure. This procedure randomly searches for a case-control match that falls within the set of defined criteria: an exact match for gender and a fuzzy match for age with a difference of 4 months (smaller age differences did not yield a match for each exposed child). We used this approach in our previous study on prenatal tobacco exposure and brain morphology (24); the same subjects were used in the current study.

Prenatal Cannabis Exposure

To optimize the cannabis exposure assessment, we used two sources of information: 1) maternal self-report of cannabis use with a questionnaire; and 2) maternal THC levels from urine. Self-reports on cannabis use during pregnancy were obtained once. In the first trimester, mothers indicated whether they used cannabis before or during pregnancy and whether they were still using cannabis, as has been described previously (4). Information about the product used and frequency of cannabis use (daily, weekly, monthly) was also available. Urine samples were collected in early, mid, and late pregnancy, and the first available sample was used for urinalysis. Urine samples were available in a subset of the cohort (4) and were tested for 11-nor-Δ9-THC-9-COOH using the DRI Cannabinoid Assay (Microgenics Corporation, Fremont, California) with a cutoff value of 50 μg/L as recommended by the manufacturer and the Substance Abuse and Mental Health Security Agency. The agreement between self-reported cannabis use and THC levels using Yule's Y was .77, indicating substantial agreement (4). Self-reported cannabis use prevalence before and during pregnancy corresponded with the prevalence of cannabis use among Dutch women aged between 15 and 64 years in the same period (27).

Prenatal Tobacco Exposure

Information about maternal smoking was prospectively obtained by postal questionnaires in each trimester (28). Maternal smoking and cannabis use were both assessed in the first questionnaire; in the second and third questionnaires, information on maternal smoking was assessed. Maternal smoking at enrollment was assessed in the first questionnaire by asking whether the mother smoked during pregnancy. In the second and third questionnaires (mid and late pregnancy), mothers were asked whether they had smoked in the last 2 months. Maternal smoking was categorized on the basis of all three questionnaires into no smoking during pregnancy, until pregnancy was known, and continued during pregnancy. The group that used tobacco until the pregnancy was known was excluded from the current study. The number of cigarettes smoked was compiled into three categories: less than 5 cigarettes per day, between 5 and 9 cigarettes per day, and more than 9 cigarettes/day (only eight pregnant mothers smoked more than 20 cigarettes per day in one of the trimesters).