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Defining the effects of prenatal cannabinoid exposure on primate fetal brain development

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Marijuana abuse during pregnancy is associated with risk for neuropsychiatric disorders in the child. Nonetheless, the impact of prenatal cannabinoid exposure on the molecular events orchestrating brain development has been intensively studied in rodents remaining unknown in primates, including humans. However, the complexity of the primate brain limits the translation of the findings from rodents to humans, urging the consideration of macaques as a model, which offers more translational advantages. Exploiting a large single-cell transcriptomic atlas resource that we generated from the prenatal rhesus macaque telencephalon, we describe the expression dynamics of the endocannabinoid signaling (ECS) pathway-related genes across monkey corticogenesis, detecting them since the earliest phases in neural progenitors. Moreover, gene expression comparison across species by transcriptomic and tissue imaging revealed differential spatiotemporal distribution of ECS-related genes in primate versus rodent developing neocortex, as they were expressed in the early neural stem cells (NSCs) in human and monkey and later in neurons in the mouse, suggesting a divergent function across evolution. Furthermore, we show preliminary data obtained from timed-pregnant monkeys upon exposure to a placebo or the cannabis psychoactive component Δ^9-THC during corticogenesis. We investigated fetal and infant subjects employing multiomics analysis from dissected regions of the brain, immunohistochemistry of brain sections and in vivo brain neuro-activity measurements including positron emission tomography (PET) and magnetic resonance imaging (MRI). This work addresses the impact of maternal cannabinoid exposure during gestation on the transcriptional and epigenetic status, and physiological activity of the offspring brain from prenatal to postnatal life.