

Karli Swenson<sup>1</sup>, Luis Gomez Wulschner<sup>2</sup>, Victoria Hoelscher<sup>2</sup>, Won Chan Oh<sup>2</sup>, Emily Bates<sup>1</sup>

<sup>1</sup> Division of Developmental Biology, University of Colorado | Anschutz Medical Campus

<sup>2</sup> Department of Pharmacology, University of Colorado | Anschutz Medical Campus

### Fetal Cannabidiol (CBD) Exposure Decreases Offspring Cognition and Alters Prefrontal Cortex Development in a Sex Dependent Manner

To diminish the debilitating nausea and vomiting of pregnancy, many pregnant people consume marijuana, or its component part cannabidiol (CBD), thinking it is safe for their developing baby. CBD diffuses down the maternal-placental-fetal pathway and cross the blood brain barrier. Retrospective clinical studies suggest that fetal marijuana exposure is associated anxiety and attention deficit and hyperactivity disorder (ADHD). However, these studies are confounded by inadequate dosing information, inability to distinguish the impact of CBD from the psychoactive marijuana component, THC, and frequent concurrent use of nicotine or alcohol. Little is known about how **fetal CBD exposure affects brain development and behavior**. To elucidate the impact of CBD exposure, we administered CBD (50mg/kg) or vehicle to pregnant mice daily from embryonic day 5 through birth. When testing offspring behavior, we found no impact of fetal CBD exposure on anxiety, memory, or compulsivity. Female CBD exposed offspring, but not males, showed decreased cognitive ability based on the puzzle box test compared to vehicle controls. To understand this decreased cognition, we analyzed serotonergic neurons from the 14-day-old prefrontal cortex, and found female, but not male, CBD-exposed offspring had electrophysiologic and morphologic changes consistent with suppressed cellular communication. To understand the transcriptional profile of these neurons, we conducted single cell RNA sequencing on the brains from the postnatal day 1.5 pups. This data revealed differences in gene expression in the biological process of learning, memory, and cognition. These results delineate sex-specific neurodevelopmental and behavioral consequences based on fetal CBD exposure. This data is critical as CBD consumption is rapidly increasing during pregnancy in the United States.