Fetal Cannabidiol (CBD) Exposure Alters Offspring Cognition and Neurodevelopment

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Goal: Determine how gestational CBD consumption effects offspring neurodevelopment and behavior

Consumption During Pregnancy is Increasing

Consumption Rates[1,2,3,4]:
- Pregnant people: 7% self reported
- Consumption increased 62% 2002 - 2014
- Highest consumption <25 years old
- Biological samples show verbal underreporting, cord blood ~22% positive

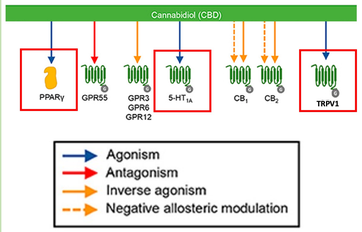
Consumption reason[5,6]:
- Nausea and/or vomiting (77.8%, 77%)
- Stress/anxiety (81.5%, 75%)
- Pain (55.1%, 83%)
- Insomnia (74%)
- Appetite (70%)

Clinical Studies of Marijuana Exposure Show Harm

Clinical studies are:
- Retrospective
- Self-reported
- Dosing is unclear
- Nonspecific to marijuana components
- Confounded with nicotine and/or alcohol

Clinical studies show[7,8]:
- Decrease in birth weight
- Increase in preterm labor
- Increase in small for gestational age
- Increase in NICU admissions
- Increased anxiety
- Increased ADHD

CBD activates receptors in the developing brain[9]



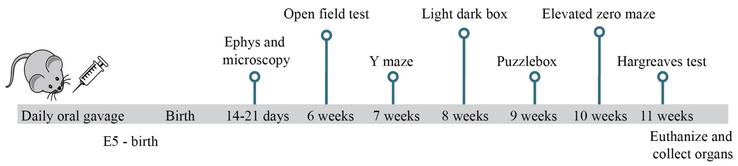
Expressed in the developing brain (including the hypothalamus)

5HT1a and TRPV1 receptor activation in-utero impacts offspring neurodevelopment

TRPV1
- Calcium permeable ion channel activated by high heat, low pH, and capsaicin
- Overactivation:
  - Impacts neural crest cell migration
  - Confers birth defects associated with maternal fever[10]

Serotonin ($5HT_{1A}$)
- Ligand gated ion channel, bound by serotonin
- Prevalent in prefrontal cortex
- Overactivation:
  - Alters neuron plasticity
  - Associated with adolescent onset of psychiatric disorders[11]

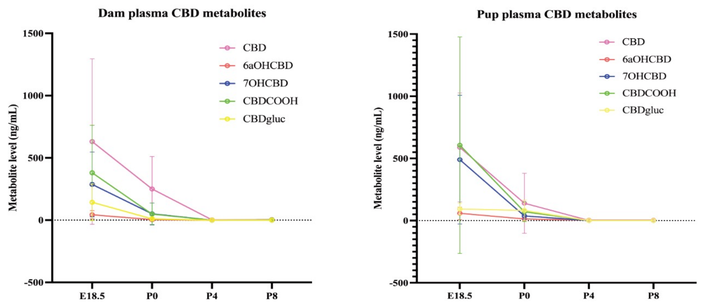
Methods



Blinding: I was blinded to which group was CBD exposed and which was vehicle until experiments were complete.

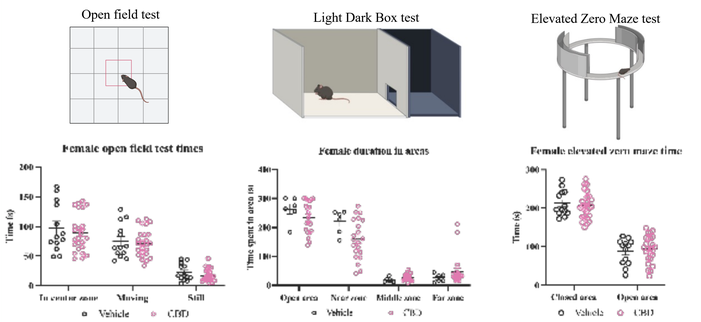
CBD metabolite validation

Dam and pup blood plasma show CBD and CBD metabolites at embryonic day 18.5 and clearing by postnatal days 4 and 8. Analysis via liquid chromatography tandem mass spectrometry.

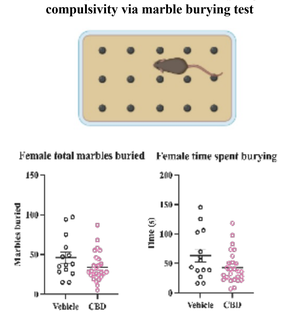


CBD exposure alters offspring thermal pain sensitivity and cognition in a sex-dependent manner, but not anxiety, compulsivity, or spatial memory

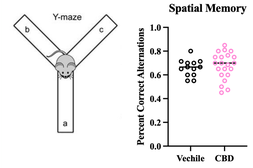
CBD exposure does not alter female nor male offspring anxiety via open field, light dark box, or elevated zero maze tests



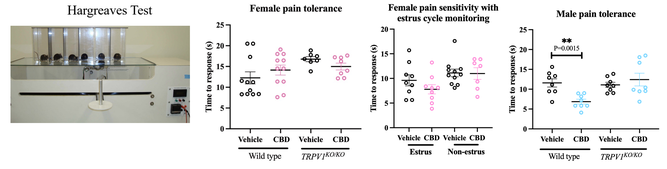
CBD exposure does not alter offspring compulsivity via marble burying test



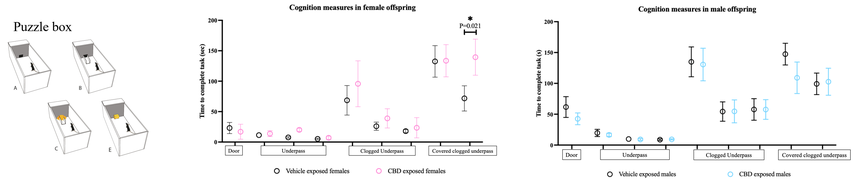
CBD exposure does not alter offspring spatial memory via Y maze test



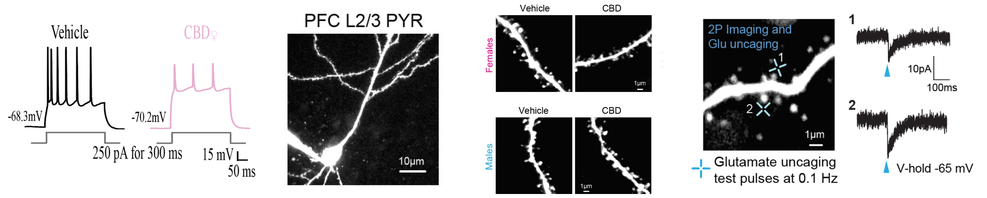
CBD exposure sensitizes male offspring to thermal pain, but not females, via Hargreaves test



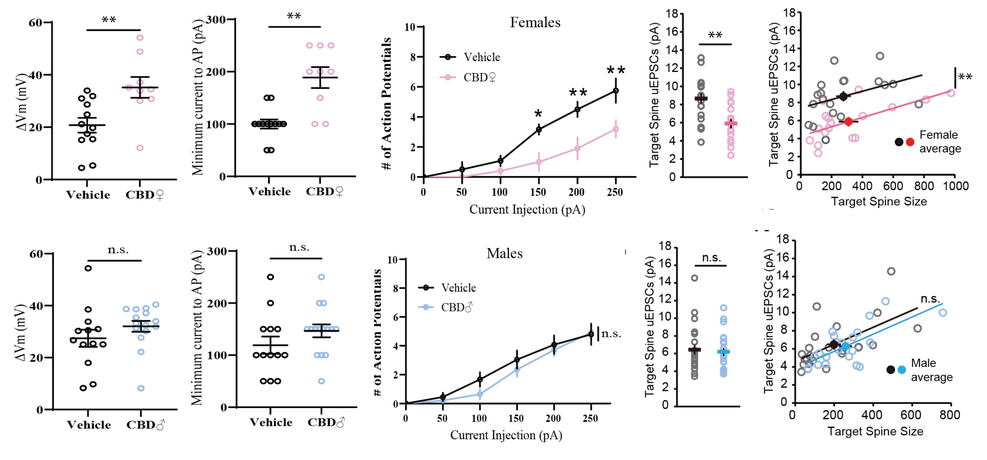
CBD exposure decreases female, but not male, cognition via the Puzzle box test



Fetal CBD exposure alters development of pyramidal neurons in the female, but not male, prefrontal cortex

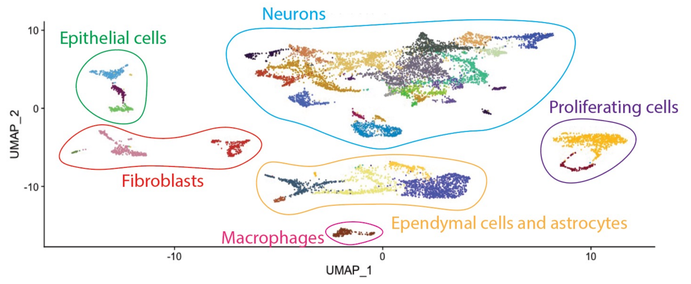


CBD exposed female offspring require higher mV and higher current to elicit an action potential, elicit less action potentials at increasing currents, have lower target spine uEPSCs, and elicit fewer target spine uEPSCs at increasing spine sizes. Male offspring show no differences based on CBD exposure.

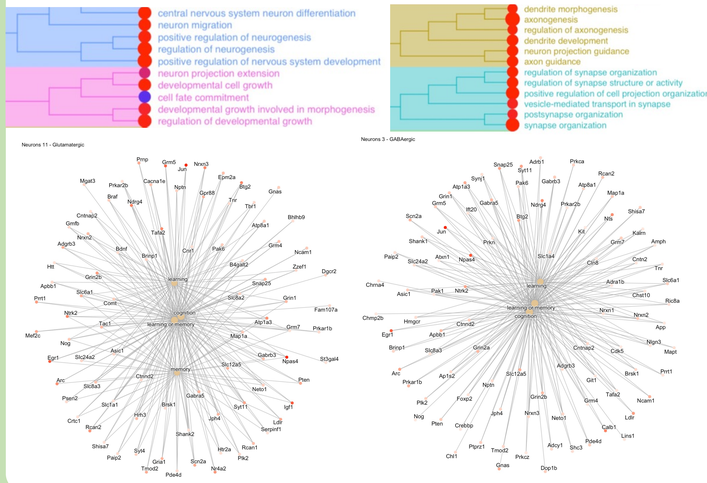


Fetal CBD exposure alters neurodevelopmental genes in the newborn hypothalamus

Postnatal day 1.5 hypothalamus dissection of two CBD exposed female offspring, two vehicle exposed female offspring, two CBD exposed male offspring and two vehicle exposed male offspring. Single cell RNA sequencing, 5,000 cells per sample, 100,000 reads per cell.



Fetal CBD exposure alters genes related to neurodevelopment, axon guidance, morphogenesis, synapse organization, cognition, learning, and other critical processes in circuit development and brain function.



Conclusions

Fetal CBD exposure:
- Does not impact offspring anxiety, compulsivity, or spatial memory
- Sensitizes male offspring to thermal pain
- Decreases female offspring cognition
- Alters pyramidal neuron development in the prefrontal cortex of female, but not male, offspring
- Alters gene regulation in the newborn hypothalamus that are involved in cognition pathways

Future work

- Understand why neurodevelopmental and behavioral findings are sex-specific
- Dose response to see if lower doses of CBD still induce behavioral and neurodevelopmental effects
- Analysis of CBD transfer through breastmilk
- Communicate with researchers, clinicians, public health professionals and the public regarding risks of consuming CBD during pregnancy

Funding: Institute of Cannabis Research, Colorado Clinical and Translational Science TL1 TR002533, Diabetes Research Center, University of Colorado Anschutz Medical Campus
IACUC approval: 139

References: 1. Ko et al 2020. 2. Jutras-Aswad, D. et al. 2019., 3. Crume et al. 2018. 4. Metz et al. 2019. 5. Dickson et al. 2018. 6. Marist Poll April 2017. 7. Hayatbakhsh, M. et al., 2012. 8. Chia-Shan Wu, et al. 2011. 9. Peres et al. 2018. 10. Hutson et al. 2019. 11. Bonnin et al. 2011. 12 McCarthy et al 2013