Perinatal exposure to cannabidiol (CBD) alters obsessive compulsive-like behavior, anxiety, and object memory in mice when raised to adult.

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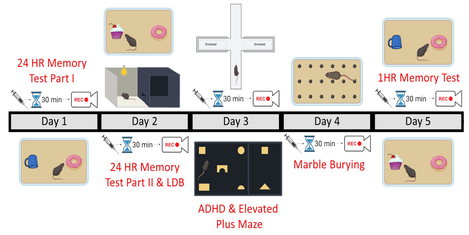
Introduction

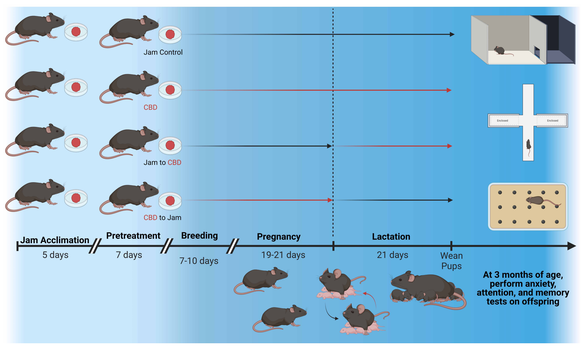
Cannabis is largely used for medicinal properties and contains over 100 phytocannabinoids, each rendering different effects on the body. **Cannabidiol** (CBD), devoid of psychoactive component, has been thought to be therapeutic to treat Parkinson's Disease, Crohn's disease, dystonia, attention-deficit hyperactivity disorder (ADHD), inflammation, depression, fibromyalgia, epilepsy, and most commonly, anxiety. The only FDA approved use of CBD, however, is for epilepsy. Like other natural plant products, the public typically envisions that CBD has health benefits, but there is a lack of significant research to support its safety and efficacy, especially during perinatal development. Women turn to CBD during pregnancy for its antiemetic and anxiolytic effects, despite the lack of studies addressing any adverse effects on the fetus. CBD is also very accessible and can be purchased without a prescription. Given the use of CBD during pregnancy, our objective was to evaluate CBD's impact on offspring that were raised to adults following perinatal exposure during both development and/or lactation. The adjoining poster from our laboratory demonstrates aspects of maternal and pup health following oral administration of CBD during pregnancy and early postnatal development. Therein we report no change in litter size, but find an increase in maternal body weight just prior to birth and an increase in pup body weight early later stages of postnatal development/lactation (P10 to P21). There was also a poor rate of pup survival to weaning age.

Herein, in our group study, we raised mice to adulthood (3 months) and then examined them in a series of behavioral phenotyping assays to determine if they were significantly altered as an adult. We want to examine molecular changes in brain regions that are resulting in this changed behavior. We also want to see if there are changes in maternal behavior that are responsible in high pup mortality by performing as assay referred to as pup retrieval. The marble burying assay is used to determine **obsessive-compulsive-like behavior** (if bury more marbles = OCD). The **light-dark box assay** (LDB) is used to determine anxiety-like behavior (if more dark location = more anxious). The **elevated plus maze** (EPM) is used to determine extreme anxiety-like behavior (if spend more time in closed arms = more anxious). The attention task is used to determine **attention deficit-like behavior** (poor recognition index = ADHD). Finally, there is a 1 and 24 hour object memory task that is used to determine **short and long-term memory** (poor recognition index = less memory).



Methods

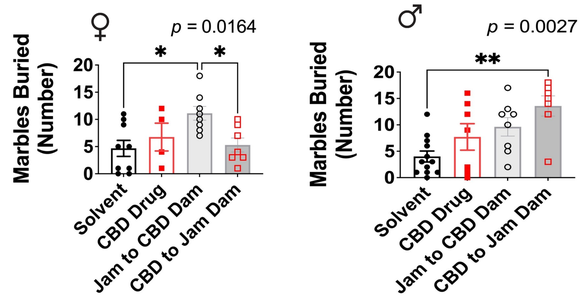
Primiparous female mice were acclimated to jam feeding for 5 days. Following this period, they were treated with 100 mg/kg CBD or control jam for 7 days, mated, and allowed a 3 week gestation period. Upon giving birth, offspring were cross fostered (from control to CBD or CBD to control) to limit influence of maternal behavior on outcomes. After 3 weeks of lactation, pups were weaned. At 3 months, offspring performed a series of behavior tests over 5 days (see introduction).



All mice used in our study were housed in the **Florida State University** (FSU) *vivaria* with a reverse 12/12-hour light/dark cycle (lights off at 8:00 A.M. and on at 8:00 P.M.). Experiments were approved under protocol number #202000036 by the FSU **Institutional Animal Care and Use Committee** (IACUC). Experiments were performed on approximately 3-month-old male and female C57BL6/J mice. Behaviors were digitally recorded and manually analyzed post-hoc.

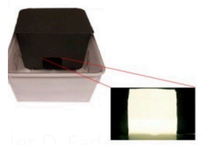
1. Early postnatal drug increase marble burying, which can be reversed by fostering to a drug-free dam for females but not for males.

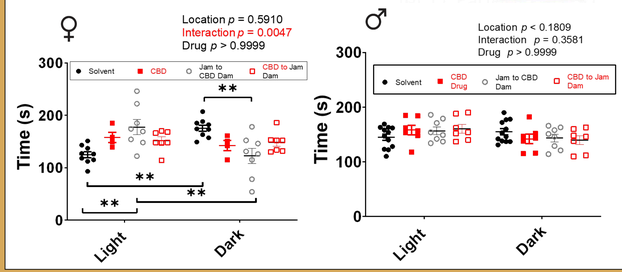
Marble Burying Test



2. CBD universally increases resident time in the light, but when adult males are administered treatments in utero they fail to exhibit a location x drug interaction.

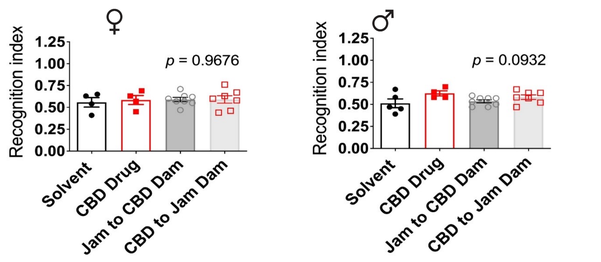
Light-Dark Box





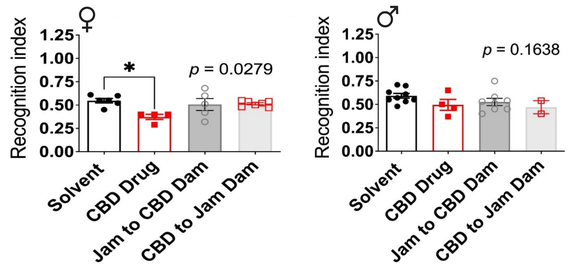
3. CBD does not affect short-term object memory of adult offspring when exposed in utero.

1-Hour Memory Test



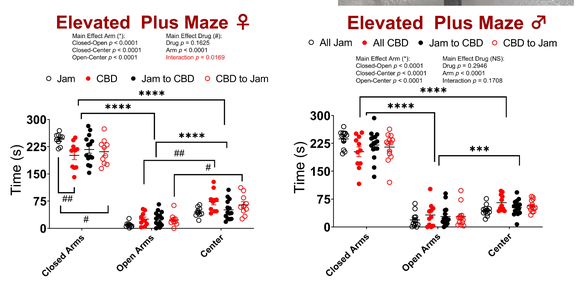
4. Female mice have reduced long-term memory following CBD treatment in utero.

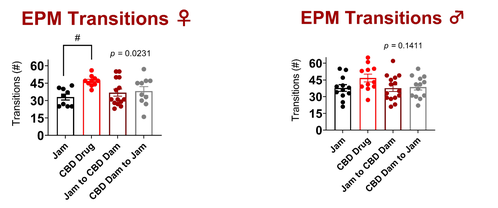
24-Hour Memory Test



5. Adult female mice spend less time in the closed arms of the maze if exposed to CBD in utero, and this is not changed with cross fostering to a drug-free dam. Males are not significantly affected.

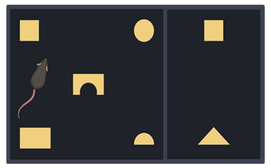
Elevated Plus Maze

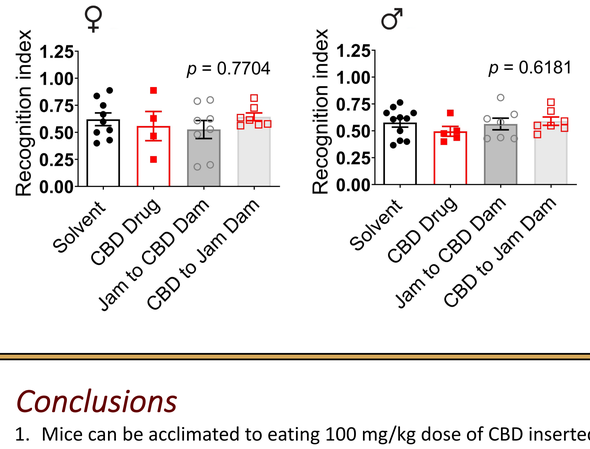




6. CBD does not affect novel object recognition of adult offspring when exposed in utero.

Object Attention (ADHD)





Conclusions

1. Mice can be acclimated to eating 100 mg/kg dose of CBD inserted into strawberry jam to provide an effective oral delivery for pregnant mice.
2. Adult mice **exhibit obsessive compulsive behavior** if exposed to CBD *in utero*. This behavior can be mitigated in females if they are cross-fostered to drug free dams but it cannot for male offspring.
3. Adult female mice **have reduced anxiety** as determined by the light-dark box when they are exposed to CBD during lactation (drug x location interaction). Adult male mice fail to exhibit a drug x location interaction in the light-dark box regardless treatment or cross-fostering condition.
4. Adult mice have a location preference in the elevated plus maze, where they prefer the closed arms. Adult female mice **are less anxious** and spend less time in the closed arms if they are exposed to CBD in utero and this **persists even if they are cross-fostered**. Male adult mice are not affected by CBD exposure in utero as determined by this measure of anxiety.
5. Adult female mice exhibit **reduced long-term object memory** when exposed to CBD in utero. This effect can be **mitigated by cross-fostering**. Neither sex exhibits reduced short-term object memory when drug exposed in utero.
6. Perinatal exposure to CBD has **no effect on performance in the object attention task (ADHD)** for either sex as an adult.

TAKE HOME MESSAGE: Use of CBD during pregnancy in mice affects OCD, anxiety, and long-term memory in a sex-dependent fashion.

References

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