RISE RESEARCH INNOVATION SCHOLARSHIP ENTREPRENEURSHIP

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Long-Term Neurobiological Implications of Adolescent Polysubstance Abuse

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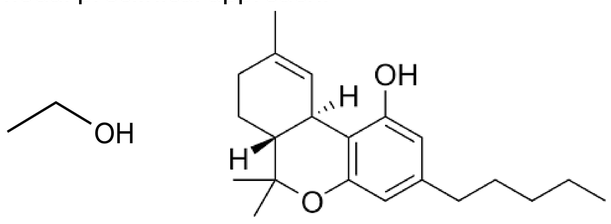
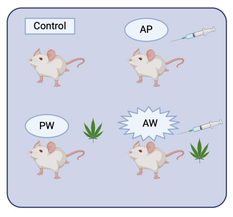
EKAM THE IMAGE OF DRUG DISCOVERY

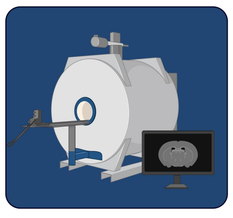
Background

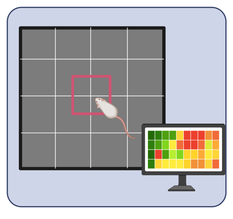
During adolescence, the brain undergoes a critical period of neuroplasticity, making it prone to developmental dysfunction. Exposure to psychoactive substances, such as tetrahydrocannabinol (THC) and alcohol, dramatically alter the way the brain develops, which subsequently affects cognition and behavior throughout adulthood. This study examines the longitudinal effects of simultaneous exposure to both substances through adulthood on neural structure and function, using a multimodal preclinical approach.



Methods







Alcohol and Cannabis Exposure

- **Day 0**: Adolescent male/female mice (N = 48) assigned to groups: PP, PW, AP, AW
- **Day 1-9**: Mice exposed to substance appropriate to group for ~ 10 day period
  - Alcohol Treatment: Mice received either ethanol (4 mg/kg) or saline placebo via oral gavage
  - Cannabis Treatment: Mice placed in box → vaporization apparatus release 10.3% THC (.475g) or placebo for 2 mins → stop exposure → let sit in box for 20 additional mins

Structural Neuroimaging

- **Day 50-52:** *Diffusion Weighted Imaging*, 7.0 T Magnetic Resonance, EPI Sequence

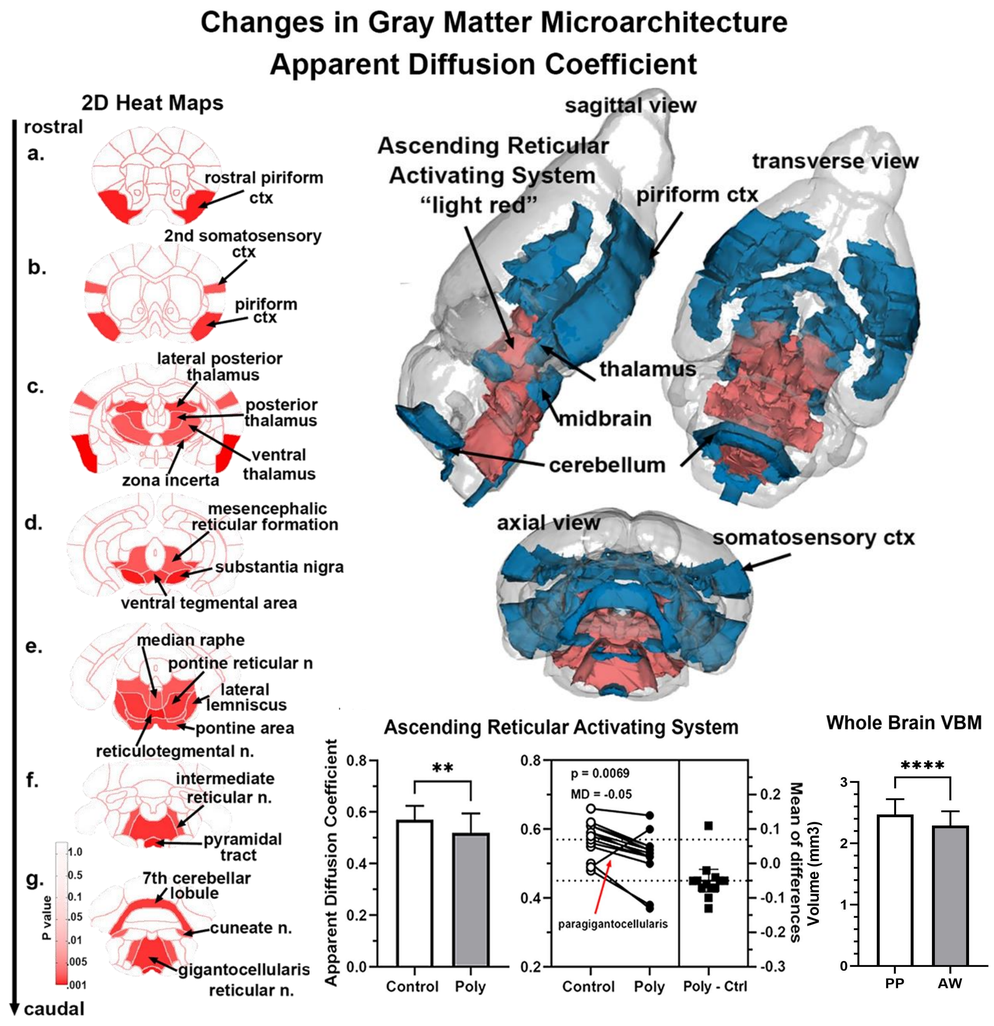
Behavior Assays

- **Day 52-54:** Open Field Test: exploratory locomotive behavior
- **Day 54 – 56:** Novel Object Recognition short-term memory

Functional Neuroimaging

- **Day 56-60:** *T2 Weighted Anatomy*, *functional Magnetic Resonance Imaging* (fMRI), *Resting State Functional Connectivity* (rsFC), 7.0 T Magnetic Resonance

Imaging Results



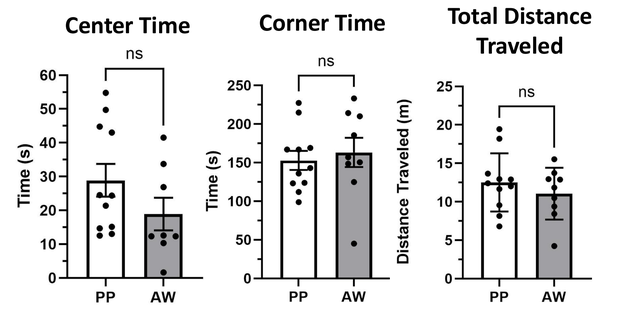
Diffusion Weighted Imaging (DWI)

- AW group experienced reduced ADC Values in the following brain regions:
  - Reticular formation → vital life abilities & stress response → prone to lethal side effects
  - Substantia Nigra → reward system activation
  - Piriform cortex → cytotoxic edema (cause of restricted water movement)

Voxel Based Morphometry

- Measures differences in the volume of neuronal cell bodies
- Significantly reduced whole brain volume in the polysubstance group

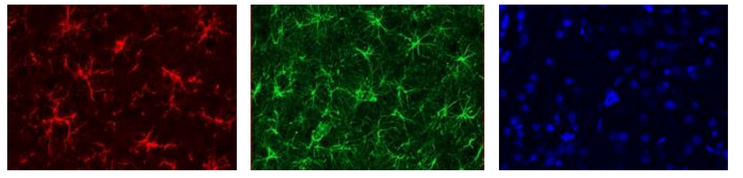
Behavioral Assays



Findings & Future Direction

Simultaneous exposure to ethanol and THC during adolescent stages of development result in reduced overall brain volume and significant changes in brain activity in later developmental stages, particularly in regions pertaining to stress response and reward activation. Some examples of future directions this project may take are:

- Conduct additional assays, such as the Barnes Maze and locomotive intoxication testing to gain a more comprehensive view of the behavioral consequences of polysubstance abuse.
- Analyze fMRI CO_2 challenge, olfactory scent, and resting-state functional connectivity (rsFC), and positive-control groups
- Histology and metabolic studies
- Further sample size to increase power analysis



Acknowledgments

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