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Undergraduate

Adolescent Polysubstance Alcohol and Cannabis Use Drives Sex-Specific Neurodevelopmental Changes

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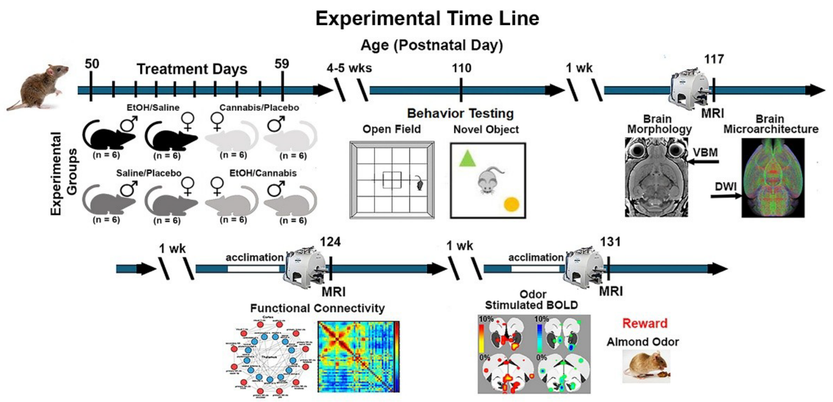
Background

Adolescence represents a critical period of neurodevelopment during which exposure to psychoactive substances such as tetrahydrocannabinol (THC) and alcohol can alter brain maturation and psychological development. This study examines the long-term neurobiological effects of simultaneous adolescent exposure to both substances in adolescent male and female mice using a multimodal preclinical MRI approach.

Methods



Subjects
Adolescent male/female mice (PND 50; N = 48, even sex split)
Treatment Groups:
PP (Double placebo); PW (Cannabis); AW (Polysubstance); AP (Alcohol)

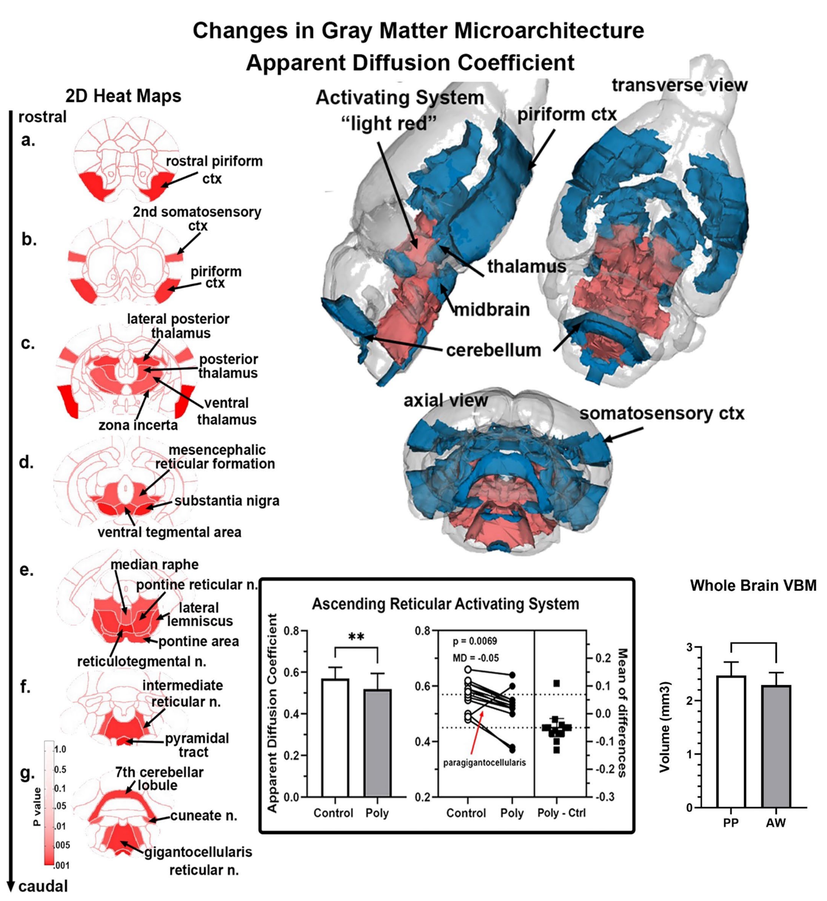
Daily Alcohol and/or Cannabis Exposure
- Postnatal Day 50-59
- Alcohol Treatment: Mice received either ethanol (4 mg/kg) or saline placebo via oral gavage
- Cannabis Treatment: Mice placed in box a vaporization apparatus released 10.3% THC (.475g) or placebo for 2 mins a stop exposure à remained in box for 20 additional mins

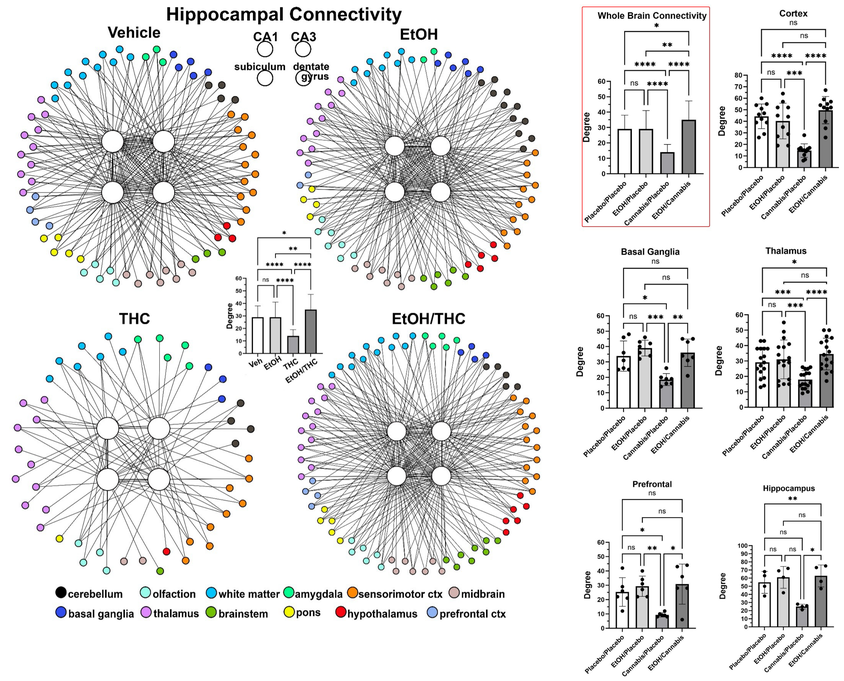
Behavior Assays
- Postnatal Day 110-111: Open Field Test assessing exploratory locomotive behavior
- Postnatal Day 112-113: Novel Object Recognition assessing short-term memory

Structural Neuroimaging
- Postnatal Day 117: 7.0 T Magnetic Resonance Diffusion Weighted Imaging (DWI) with EPI Sequence to assess structural neural changes

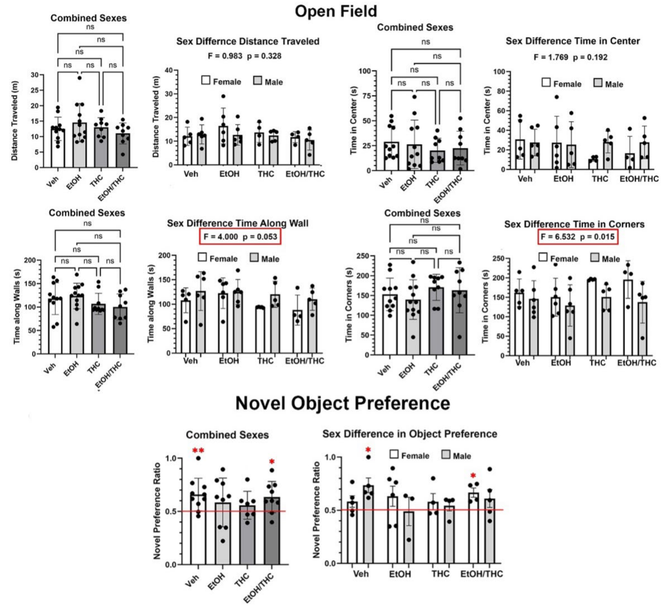
Functional Neuroimaging
- Postnatal Day 124-131: 7.0 T Magnetic Resonance T2 Weighted Anatomy, functional Magnetic Resonance Imaging (fMRI), Resting State Functional Connectivity (rsFC)

Neuroimaging





Behavior



Discussion

· Polysubstance co-exposure produced the greatest microstructural disruption, with elevated ADC values in the ARAS, including the mesencephalic reticular formation, substantia nigra, and ventral tegmental area, indicating a non-additive interaction; despite this, resting-state fMRI showed preserved connectivity, underscoring the need for multimodal imaging.
· Effects were sex-dependent: alcohol alone reduced gray matter volume in males, while co-exposure shifted vulnerability toward females,
· Sex-specific differences in exploration and short-term memory, highlighting sex as critical in polysubstance research.

Conclusion

Adolescent co-exposure to alcohol and cannabis produces distinct neurobiological effects that differ from either substance alone, shifting volumetric risk from males to females, preserving functional connectivity despite structural injury, and uniquely impacting the ascending reticular activating system. These results show that co-exposure of drugs is not necessarily a combination effect, and that recognizing sex-specific differences is critical for targeted prevention and intervention.

Acknowledgments

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