Changes in brain structure and function following exposure to oral psilocybin during adolescence in female and male mice: A multimodal MRI study

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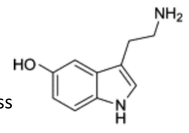
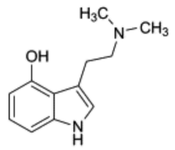
Introduction

In recent years, psychedelics have seen a resurgence in research for their potential in treating psychiatric disorders including major depressive disorder and post-traumatic stress disorder. Despite being classified as a Schedule 1 substance during the War on Drugs, recent studies are re-examining the effects of psilocybin, a potent 5-HT2A agonist, on brain function. Amidst this renaissance of psychedelic therapeutic research, our study examines the long-term effects and potential risks of exposure to psilocybin during adolescence, a vulnerable period of rapid neurodevelopment. The results of this investigation suggest a long-lasting impact on brain structure and behavior, sparking further interest in its long-term neuroplastic effects.



Serotonin



Psilocin

Experimental Design

Adolescent male and female mice (18-22 g) were divided into groups receiving either vehicle (*n*=12) or psilocybin (*n*=12) treatment. Multimodal MRI and behavioral assays were conducted 3-4 weeks later in adulthood. Animals were housed on a reverse light-dark cycle with all procedures carried out under dim red-light illumination for ecological validity of circadian rhythms.

Postnatal Day 51

Treatment via Oral Gavage

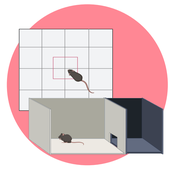
- 3.0 mg/kg psilocybin via 100 µl oral gavage *or* equivalent saline dose via 100 µl oral gavage
- 5 doses over 10 days

Postnatal Day 81

7T Magnetic Resonance Imaging (MRI)

- **T2-weighted Anatomical Scan** for global and site-specific analysis of volumetric changes to brain regions via Voxel-Based Morphometry.
- **Diffusion Weighted Imaging (DWI)** for global and site-specific analysis of microstructural changes to brain regions. Fractional Anisotropy (FA) is a standardized measure of the degree of restriction of water movement in tissue.

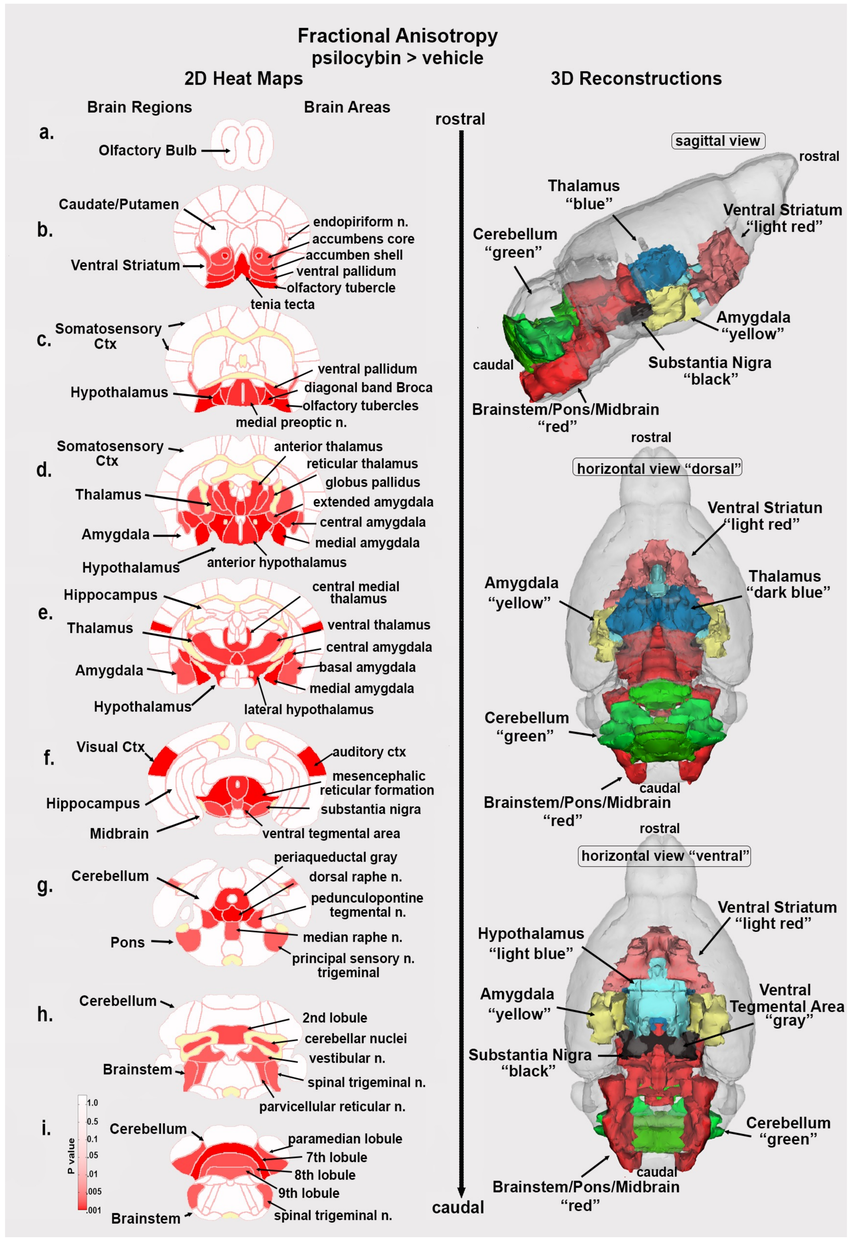
Postnatal Day 90



Cognitive Behavioral Assays

- **Open Field Test (OFT)**: Indicators of exploratory locomotor activity in mice include distance traveled, average speed, and center crossings in a novel arena.
- **Light-Dark Box Test**: Indicators of anxiety-like behavior in mice include time spent in the stressful context (light box), time spent in the safe context (dark box), and entry frequency.

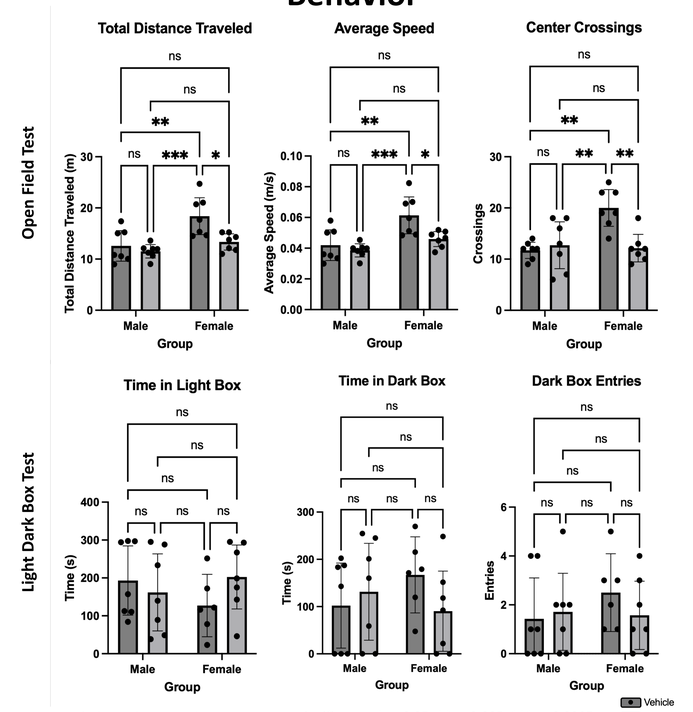
Psilocybin Exposure in Adolescence Results in Lasting Changes to Gray Matter Microarchitecture



Diffusion Weighted Imaging (DWI) conducted in adulthood, 3-4 weeks after adolescent psilocybin exposure, indicates lasting significant changes in gray matter microarchitecture globally and regionally. FA was broadly increased throughout the midbrain and hindbrain, indicating cytoarchitecural changes restricting isotropic movement of water through brain tissue. This is likely indicative of changes in small vessel architecture, gray matter myelination, and glial cell populations.

Data were registered to a mouse brain atlas and segmented into 174 brain regions for analysis. The FA value of each region was compared across conditions via non-parametric Kruskal-Wallis test and statistically significant regions ($p < 0.05$) are shown in red on the 2D heat maps above at left. 3D structure of affected regions is shown above at right. Statistically significant changes in apparent diffusion coefficient, axial diffusivity, or radial diffusivity were minimal.

Psilocybin Exposure in Adolescence Results in Sex-Dependent Changes in Exploratory Behavior



Independent samples t-test: n.s. no significance; * p<0.05; ** p<0.005; *** p<0.0005

OFT: A sex-dependent difference was observed in control mice, with females exhibiting greater exploratory locomotor behaviors than males. In psilocybin-exposed females, exploratory behavior was significantly reduced to the levels seen in males.

LDB: No significant differences were observed.

Concurrent & Future Studies

- **Resting-State Functional Connectivity (rsFC)**: Preliminary results indicate lasting hyperconnectivity of thalamocortical circuitry
- **Sex Differences**: Studies with larger sample sizes will improve statistical power and enable analysis of sex differences in brain structure and individual variability
- **Repetitive Mild Traumatic Brain Injury**: Expanding the existing literature on psilocybin as a therapeutic to include treatment of rmTBI
- **Comparative Studies**: Comparing psilocybin to other treatment modalities, including non-hallucinogenic 5-HT2A agonists, will provide a comprehensive understanding of its therapeutic potential
- **Personalized Medicine**: Future research should account for individual factors including genetics and mental health history to develop personalized treatment strategies

Acknowledgments

- **Psilocybin:** National Institute on Drug Abuse
- **Funding:** Ekam Imaging

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