RISE RESEARCH INNOVATION SCHOLARSHIP ENTREPRENEURSHIP

Submission ID: 238
Mentor Name: Craig Ferris
Category: Health Sciences
Undergraduate

Northeastern University

Neurobiological Changes Following Adolescent Exposure to LSD in Mice: An MRI Study

D.S. ATHREYA[1], L.M. HARRIS[1], Z. SMITH[1], A. CHANG[1], R.J. ORTIZ[2], P.P. KULKARNI[1], C.F. FERRIS[1]

Northeastern University
Center for Translational Neuro-imaging

[1]Center for Translational Neuroimaging, Northeastern University, Boston, MA
[2]Department of Chemistry and Biochemistry, New Mexico State University, Las Cruces, NM

EKAM THE IMAGE OF DRUG DISCOVERY

Background, Rationale, and Approach

During the War on Drugs in 1971, the United Nations classified LSD as a Schedule 1 substance. In the past decade, there has been a resurgence of scientific interest in LSD. Small clinical trials report promising results in treating MDD, PTSD, and alcoholism. How does LSD alter brain neural circuitry to affect behavior? Does exposure to LSD in adolescence have long-lasting effects on brain structure and function? We studied male and female mice exposed to LSD during neurodevelopmental adolescence for changes in neurobiology in adulthood using multimodal MRI and behavior assays testing for motor control, cognitive function, and anxious presentation.

Methods

Experimental Design

Male and female mice (18-22 g) were exposed to vehicle (n=12), a single oral dose of LSD (n=12), or six doses spread over two weeks (n=11) starting on postnatal day 51. Each dose was equivalent to 3.3 µg LSD. All experiments were conducted under dim red illumination between 10:00 hrs and 18:00 hrs to avoid the disruptions in circadian rhythms.

Imaging/Analysis

Mice were imaged using a 7T scanner and behavior was tested at postnatal days 90 – 150 (young adulthood). Data from voxel-based morphometry (VBM), diffusion weighted imaging (DWI), and BOLD rsFC were registered to a mouse 3D MRI atlas with 140 brain regions. DWI using measures of apparent diffusion coefficient (ADC) was used to surmise changes in gray matter microarchitecture.

Results

Voxel Based Morphometry

Area-specific changes in brain volume were few.

Diffusion-Weighted Imaging

Male and female mice exposed to LSD multiple times in adolescence presented with dramatic changes in gray matter microarchitecture over many brain areas as compared to vehicle and single dose treatments.

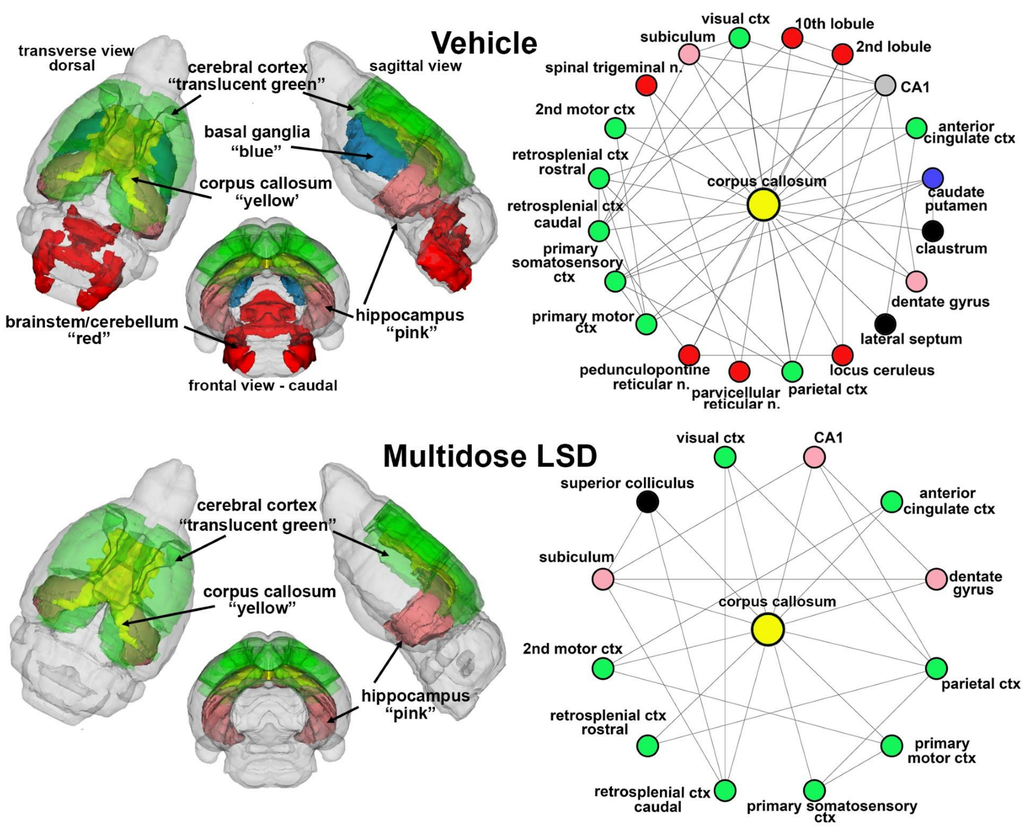
Functional Connectivity

BOLD resting state functional connectivity was not significantly different across brain areas except for the connectivity to the corpus collosum. LSD reduced connectivity to brainstem cerebellum and basal ganglia.

Behavior

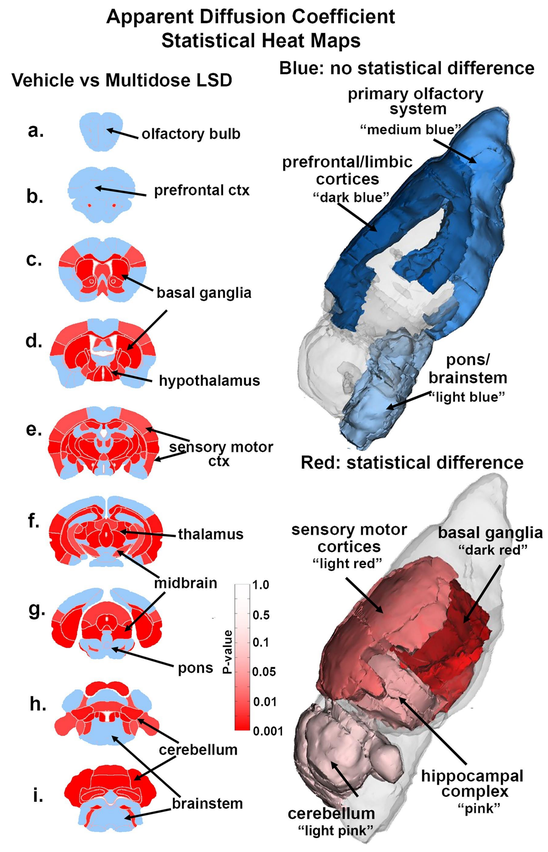
Tests in the open field and novel object preference for multidose exposure were unremarkable; however, a single dose of LSD did increase time in the center.

Resting State Functional Connectivity



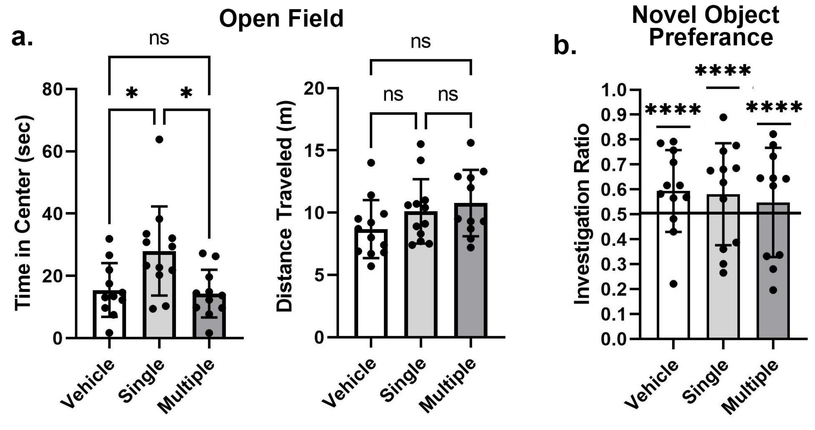
Shown above are LSD-induced developmental changes in connectivity to the corpus callosum

Diffusion-Weighted Imaging



Shown above are heat maps and 3D reconstructions summarizing the LSD induced developmental changes in gray matter microarchitecture using DWI.

Behavior



Mice exposed to a single dose of LSD spent significantly more time in the center of the open field than vehicle or multiple dose treatment. There were no significant differences between groups for distance traveled or novel object preference.

Questions and Further Research

Would the observed changes persist through end-of-life?

Longitudinal imaging through adulthood

How would dose variation affect the results?

Replicate with low, medium, and high doses

To what extent does repetition increase risk?

Replicate with more multi-dose treatment groups

Limitations

- Single dose of LSD without brain or blood levels.
- Need for a greater battery of behavioral tests.
- These studies were limited to 30 days post exposure to a single concentration of LSD

Acknowledgement: We thank the National Institute on Drug Abuse for providing the LSD and Ekam Imaging for supporting these studies.