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

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Background, Rationale & Approach

Amidst the War on Drugs in 1971, the United Nations classified LSD and other psychedelic drugs as Schedule 1 substances. However, in the past decade, there has been a resurgence of scientific interest in LSD. Small clinical trials report promising results in treating MDD, end-of-life distress, PTSD, and alcoholism. We aim to investigate how LSD alters neural circuitry, specifically the long-term effects of exposure to LSD during adolescence on brain structure and function. We orally administered LSD to male and female mice during neurodevelopmental adolescence to assess changes in neurobiology in adulthood through multimodal MRI and behavior assays testing for motor control, cognitive function, and anxious presentation.

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). All mice were given an oral gavage of a 100 µl solution, equivalent to 3.3 µg LSD. All treatments started on postnatal day 51 . All experiments were conducted under dim red illumination between 10:00 hrs and 18:00 hrs to avoid the disruptions in circadian rhythms. 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.

Summary

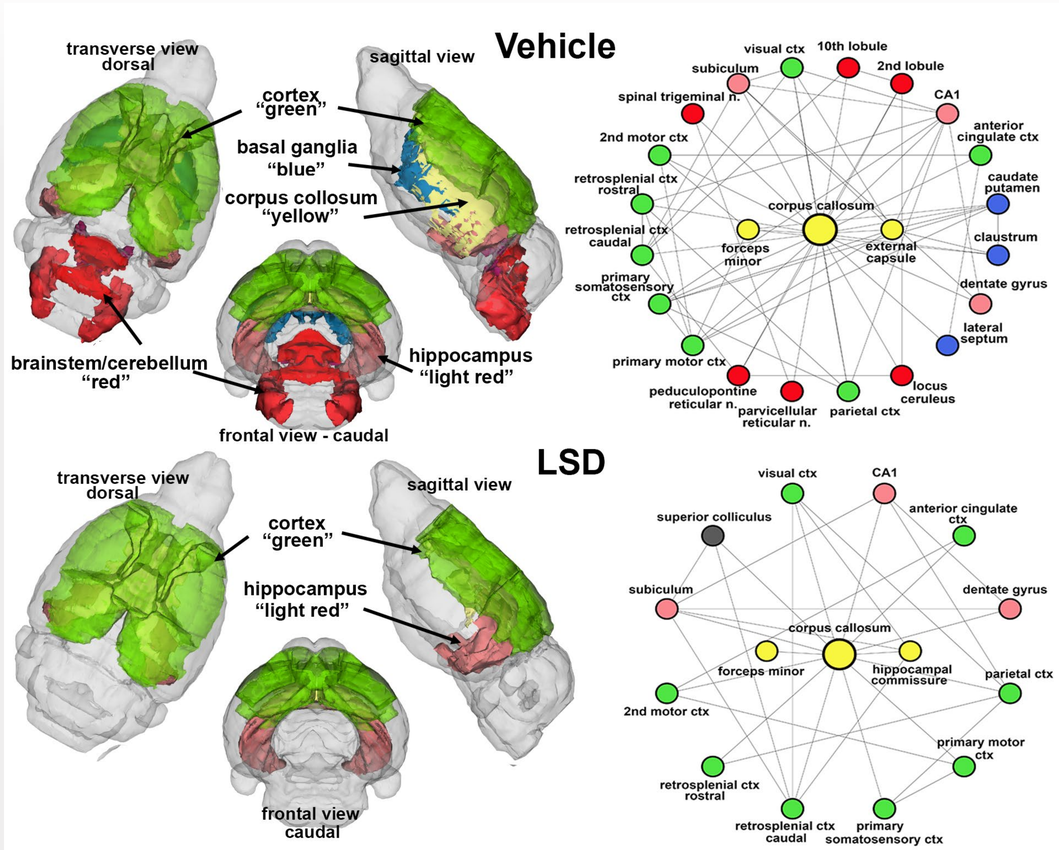
Male and female mice exposed to LSD multiple times in adolescence presented with dramatic changes in gray matter microarchitecture over many brain areas as compared to vehicle and single dose treatments. Area specific changes in brain volume were few. BOLD resting state functional connectivity was not significantly different across brain areas except for the connectivity to the corpus collosum. LSD reduced connectivity to brainstem/cerebellum and basal ganglia. Tests in the open field and novel object preference for multidose exposure were unremarkable; however, a single dose of LSD increased time in the center.

Limitations

- Dose-dependent factor remains unknown.
- Need for a greater battery of behavioral tests.
- These studies were limited to 30 days post exposure to a single concentration of LSD. Are the observed neural changes permanent to end-of-life?

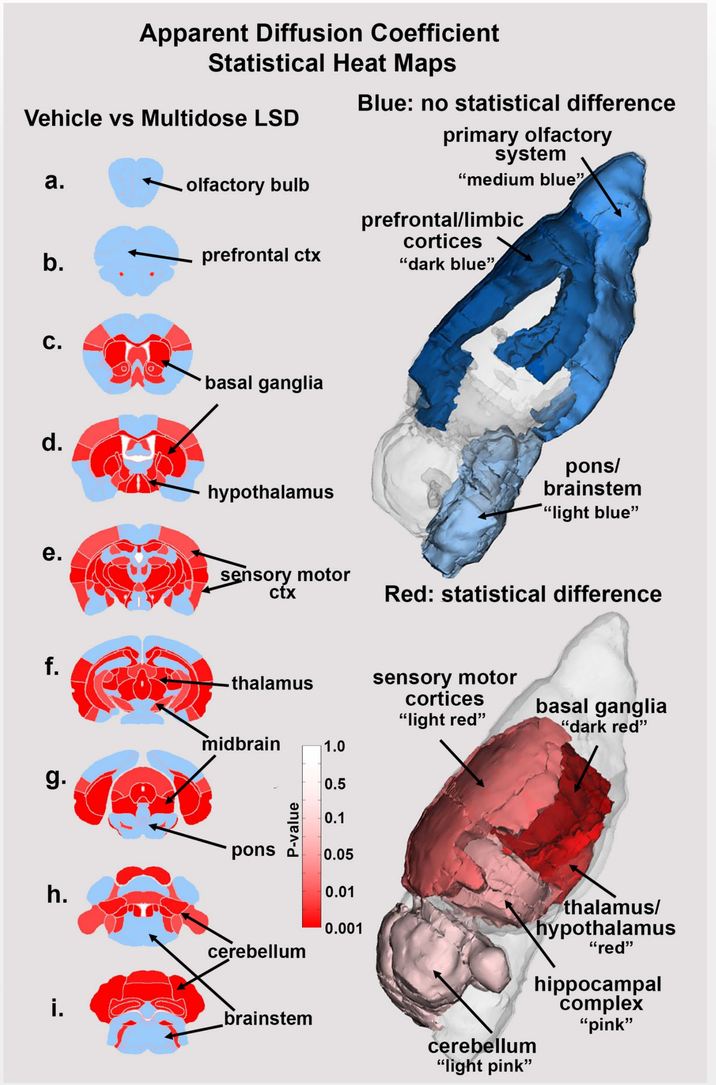
Results

Resting State Functional Connectivity



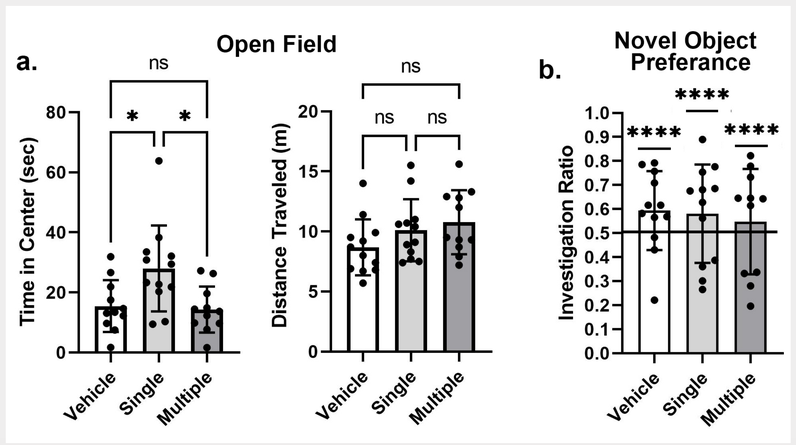
Shown above are LSD-induced developmental changes in connectivity to the corpus callosum

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 veh or multiple dose treatment. There were no significant differences between groups for distance traveled or novel object preference.

Voxel Based Morphometry

Brain Area	Control Ave	Control SD		LSD Ave	LSD SD	P val	Ω Sq
auditory ctx	3.29	0.47	<	4.02	0.53	0.005	0.324
lateral paragigantocellular n.	1.28	0.29	<	1.51	0.19	0.024	0.187
6th cerebellar lobule	4.15	0.52	<	5.03	1.12	0.029	0.173
cortical amygdaloid n.	3.73	0.58	<	4.28	0.58	0.031	0.167
fimbria hippocampus	2.28	0.13	>	2.16	0.13	0.039	0.150
secondary somatosensory ctx	5.48	0.43	>	5.13	0.44	0.049	0.132

Multiple doses of LSD during adolescence do not affect brain volume in young adult mice. (FDR – false discovery rate)

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