RISE RESEARCH INNOVATION SCHOLARSHIP ENTREPRENEURSHIP

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Changes in Brain Activity Following LSD Exposure: MRI Study in Awake Rats

EKAM THE IMAGE OF DRUG DISCOVERY

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Background, Rationale & Approach

Amidst the War on Drugs in 1971, the United Nations classified lysergic acid diethylamide (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. Animal studies report that low doses of LSD act through 5HT2a receptors to decrease anxiety and promote prosocial behavior [3], while higher doses also alter dopaminergic signaling, causing cognitive dysfunction. How does LSD alter brain neural circuitry to affect behavior? To address this question, we used BOLD imaging to follow changes in brain activity in male and female rats exposed to LSD.

Experimental Design

Awake male and female adult rats were exposed to veh (n=5) , 10ug/kg (n=5) or 100 ug/kg (n=6) of LSD during the 35 min scanning session followed by resting state functional connectivity. Images were registered to, and analyzed, using a 3D MRI rat atlas providing site-specific data on 173 different brain areas. All experiments were conducted under dim red illumination between 10:00 hrs and 18:00 hrs to avoid the transitions between the L-D dark cycles. Rats were acclimated to the awake imaging protocol for five days before imaging. Scanning was conducted on a 7T small animal scanner (see below).

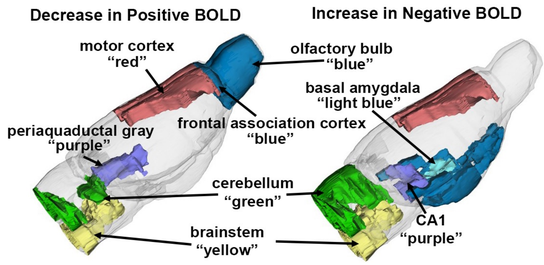
Summary

Awake, drug naïve rats exposed to LSD during the scanning session showed a dose-dependent change in BOLD signal. Low dose LSD reduced brain activity while high dose LSD increased activity in the hindbrain while decreasing activity in the forebrain. High dose LSD enhanced functional connectivity between thalamus and cortex. There was an unexpected increase in cerebellar connectivity and efferent connections to the whole brain.

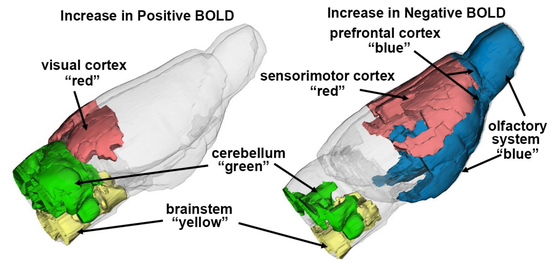
Unanswered Questions

- **Does the general decrease in brain activity to low dose LSD contribute to the anxiolytic effects of this hallucinogen?**
- **Does the increased activity in the brainstem reticular activating system and cerebellum together with a loss of activity in the somatosensory and prefrontal cortices represent dissociation?**

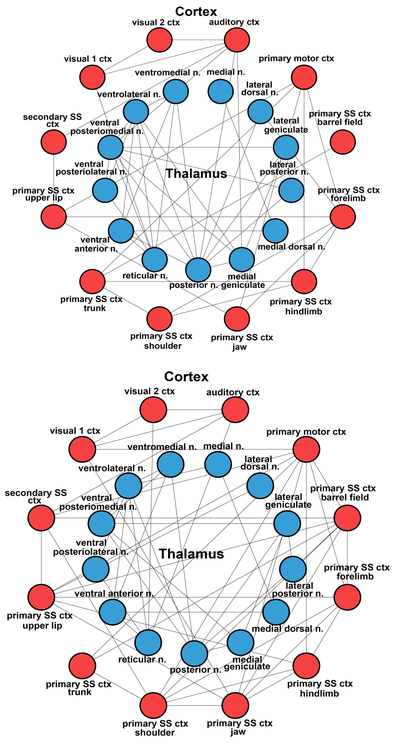
Low dose LSD (10ug/kg) decreases activity in the brainstem/cerebellum, motor cortex and olfactory system.



High dose LSD (100ug/kg) activates brainstem/cerebellum but reduces activity in the sensorimotor and prefrontal cortices and the olfactory system

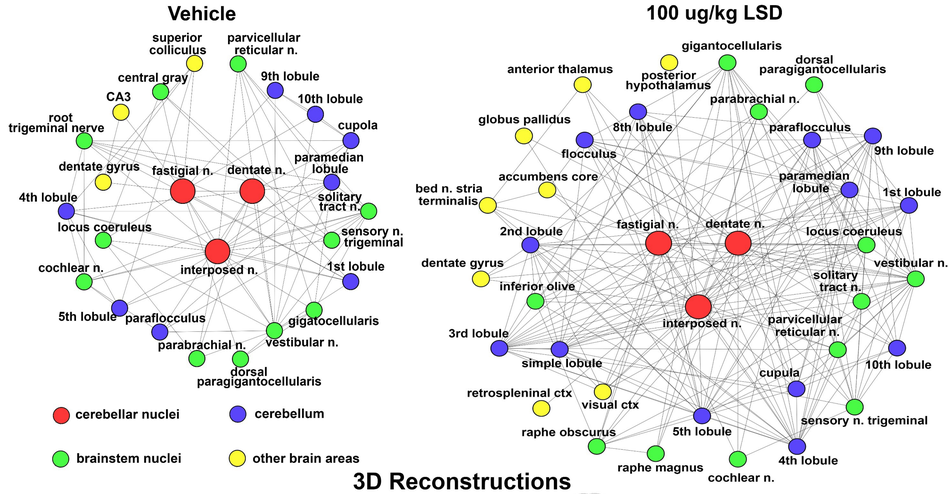


LSD enhanced thalamic/cortical connectivity

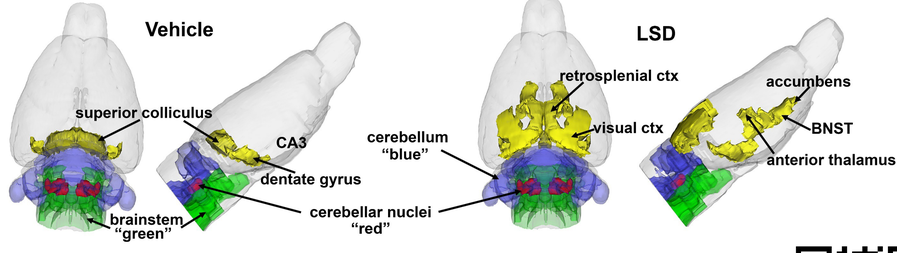


BOLD Resting State Functional MRI

LSD enhances cerebellar functional connectivity



3D Reconstructions



Acknowledgement

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