Dose-dependent Changes in Olfactory, Cortical/Thalamic and Cerebellar Activity Following Exposure to LSD: a BOLD MRI Study in Awake Rats

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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.[4,5] Animal studies report that low doses of LSD act through 5HT2a receptors to decrease anxiety and promote prosocial behavior[6], 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.

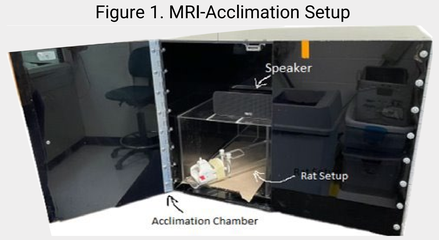
Experimental Design

Awake male and female adult rats were exposed to Vehicle, 10µg/kg, or 100 µg/kg of LSD (Table 1) 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 and 18:00 hrs to avoid the transitions between the light-dark cycles. Rats were acclimated to the awake imaging protocol for five days before imaging (Figure 1). Scanning was conducted on a 7T small animal scanner.

Table 1. Design of the Study

Group	Dosage (IP)	Sample Size
Vehicle	0 µg/kg	5
Low Dose	10 µg/kg	5
High Dose	100 µg/kg	6

Figure 1. MRI-Acclimation Setup



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?

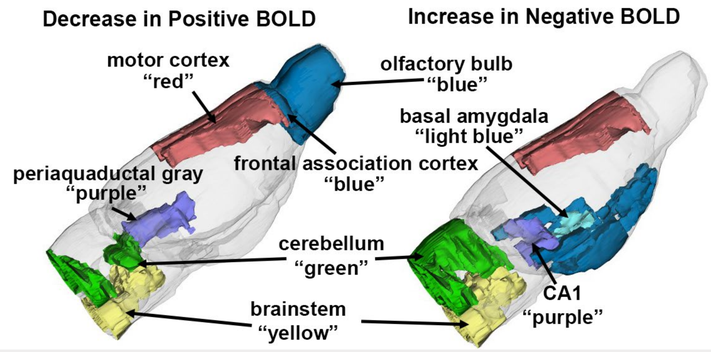
Acknowledgement

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

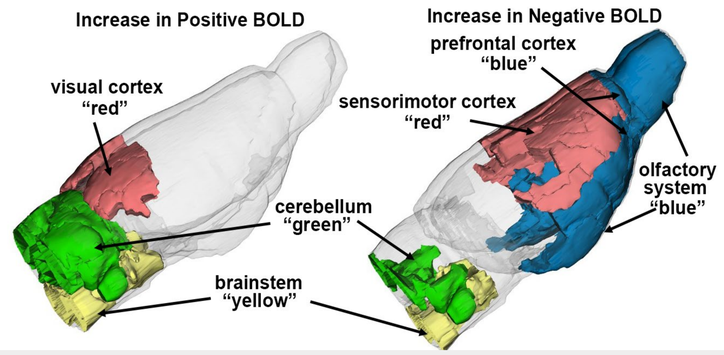
Results

BOLD Pharmacological Functional MRI

Low dose LSD decreases activity in the brainstem/cerebellum, motor cortex and olfactory system.

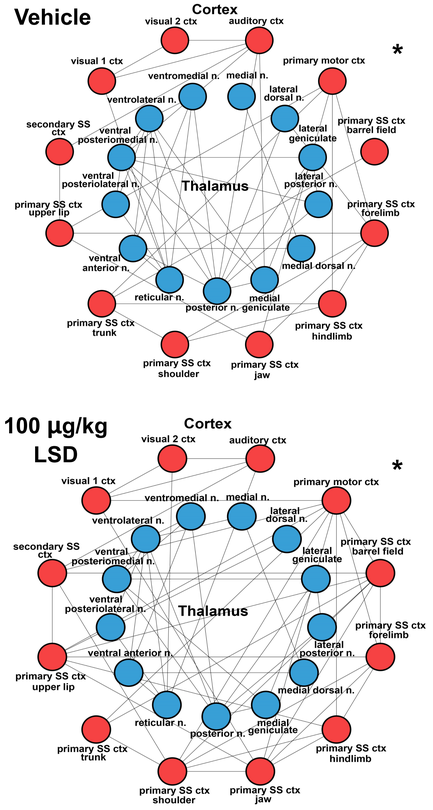


High dose LSD activates brainstem/cerebellum but reduces activity in the sensorimotor and prefrontal cortices and the olfactory system

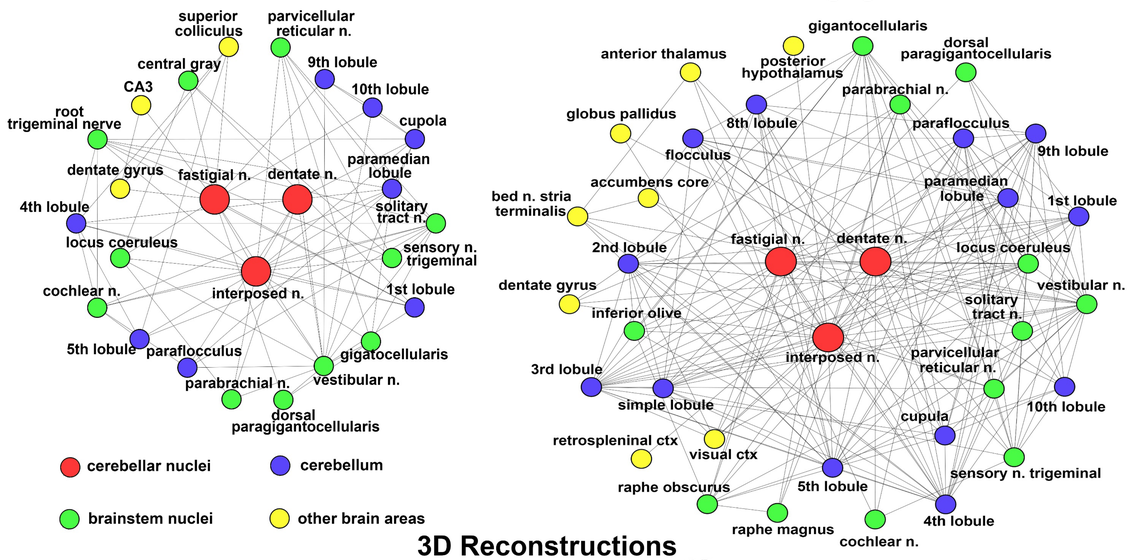


BOLD Resting State Functional MRI

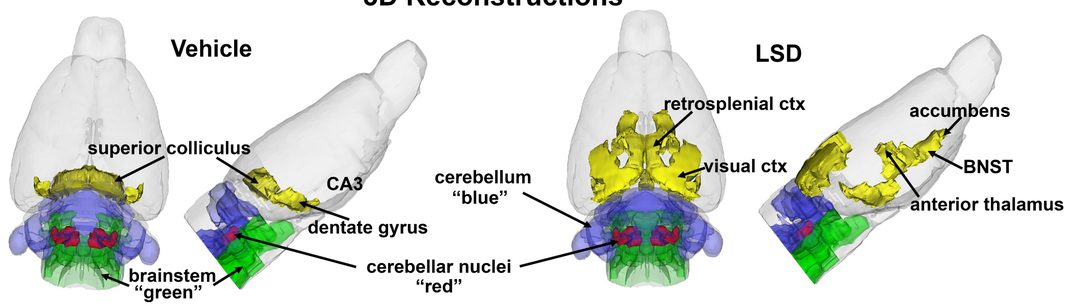
LSD enhanced thalamic/cortical connectivity



LSD enhances cerebellar functional connectivity



3D Reconstructions



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