Ibogaine Induced Dose-Dependent Changes in Global Brain Activity and Connectivity Using fMRI

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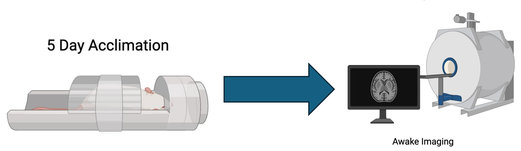
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INTRODUCTION

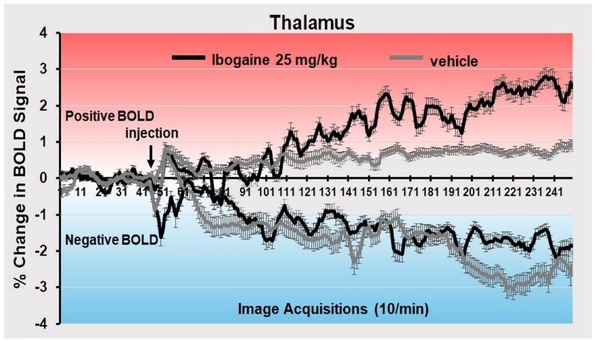
Ibogaine is a naturally occurring alkaloid from the root bark of the Tabernanthe iboga shrub with traditionally ritualistic use. Broad pharmacology shows interactions with Sigma, Serotonin, Opioid and NMDA receptors, and it is known to cause Hallucinogenic effects. A dose-response project was conducted with rats studying global brain activity using fMRI and resting state functional connectivity on fully awake male and female rats. The goal of this study was to map brain areas that may show any changes after Ibogaine injection.

METHODS

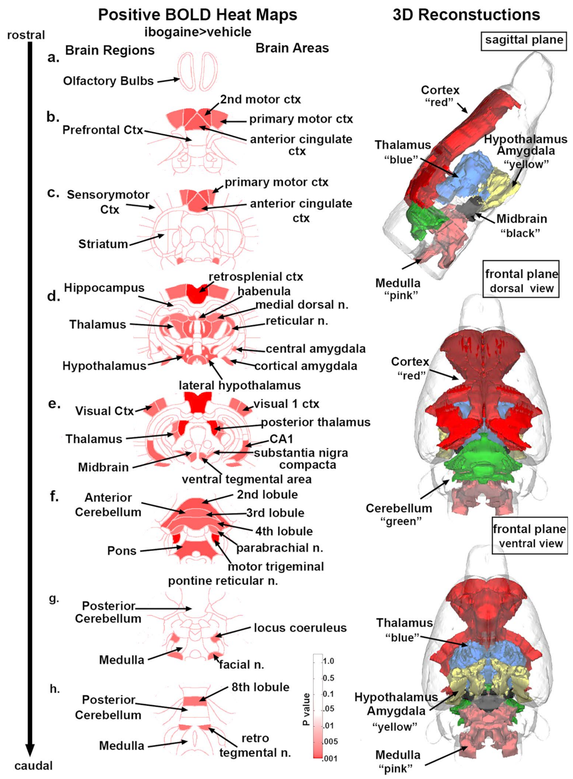
- Animal Model: The experiment included 48 rats (24 male, 24 female) that were divided into 4 cohorts. Each received doses measured as Vehicle (VEH), 1 mg/kg (Low), 5 mg/kg (Med) and 25 mg/kg (High) of Ibogaine HCl, with 12 rats (6 male, 6 female) in each cohort.
- Acclimation: The rats were first subjected to 5 days of acclimation before scanning. Scanning was 45 minutes total, and included a T2 anatomy scan first, followed by a Functional MRI scan, with lastly a resting state functional connectivity scan.
- Study Drug: Ibogaine was administered 5 minutes into the scan via IP injection. Both acclimation and scanning was conducted using reverse L/D cycles to maintain the natural circadian rhythms of the rats.
- Imaging: Brain imaging used a 7.0 Tesla Bruker Biospec horizontal magnet, with image analysis being broken up into 3 stages; pre-processing, processing, and post-processing.
  - Pre-processing; Pre-processing consisted of denoising due to unwanted movement and hardware results, and skull stripping to remove non-brain tissue.
  - Processing: The data from the imaging scans of each subject was aligned to a 3D Rat brain model via Atlas and mapped to each anatomical brain location using voxels assigned to a brain region.
  - Post-Processing: The activated voxels in 169 of the brain areas was measured and compared across the Vehicle and Ibogaine doses.
- Statistical Analysis: Analysis was done by recording BOLD signal changes that differed by ±1% from the Vehicle baseline following IP injection. After these values were retained following processing, they were assigned to each of their 169 regions by voxel and the changes in activity were measured.



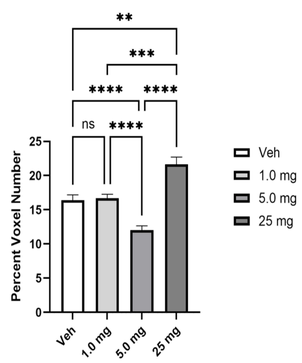
BOLD Response Time Course in the Thalamus



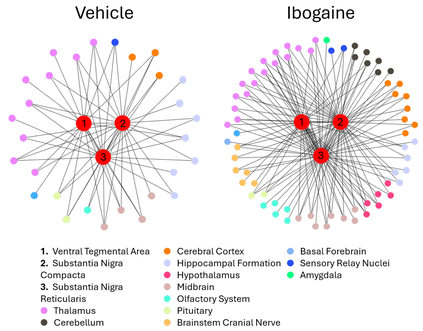
Positive BOLD Heat Maps



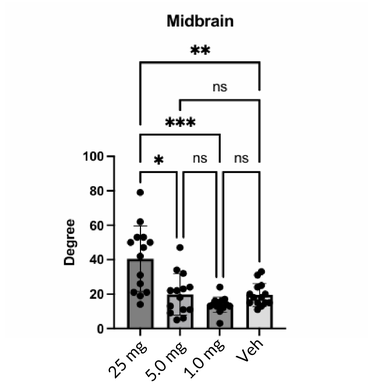
Ibogaine Brain Dose Response Normalized



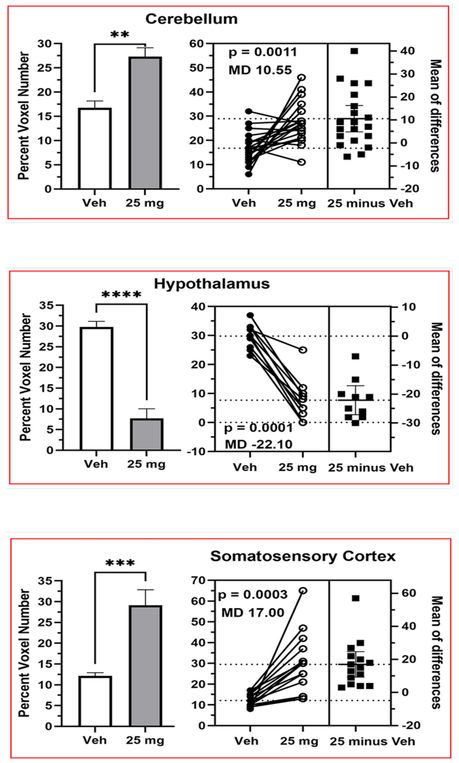
Ibogaine High Dose Universe Plot



Midbrain Dose Response



Percent Voxel Number Difference Between Vehicle and High Dose



RESULTS

Pharmacological fMRI

- Significant Positive BOLD response greater than VEH, negligible Negative BOLD response

Resting State Functional Connectivity

- Ibogaine increases activity in the motor cortex, without activation of the Hypothalamus

Dose-Response

- Low-Dose decreases connectivity to the Midbrain
- High-Dose engages the Cerebellum

CONCLUSIONS

- Significant Positive BOLD response following injection denotes substantial increase in blood flow.
- Positive BOLD heat map points to an increase in blood flow and activation in the Thalamus.
- Ibogaine Dose Response indicates a Non-Monotonic pattern from Low dose to High dose, with comparable voxel numbers between Vehicle and low dose while the High dose sees a major increase in voxel activity.
- Injections of the High dose of Ibogaine triggered connectivity in the Ventral Tegmental Area, the Substantia Nigra Compacta and the Substantia Nigra Reticularis to other areas of the brain, indicating neural stimulation,
- Decreased activity in the Midbrain following a Low dose, but an increase with each subsequent dose.
- High dose of Ibogaine saw an increase in engagement with the Cerebellum and Somatosensory Cortex, with a decrease in connection to the Hypothalamus.

FUTURE DIRECTIONS

Behavioral Tests to assess potential for substance-abuse mitigation;

- Conditions Placed Preference Tests (Reward Stimuli)
- Intravenous Self-Administration Tests (Addiction)
- Craving Incubation Tests (Relapse)

Can be applied to anti-addiction treatments:

- Opioid-Use Disorder
- Alcohol-Use Disorder

ACKNOWLEDGEMENTS

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NIDA Advancing Addiction Science 50 years

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