RISE RESEARCH INNOVATION SCHOLARSHIP ENTREPRENEURSHIP

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

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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.

Conclusion

The results of this study revealed that rats injected with Ibogaine exhibited substantial activity in the Ventral Tegmental Area, the Substantia Nigra Complex, and the Substantia Nigra Reticularis as compared to the Vehicle rats. These areas saw new connections to the Cerebellar cortex, the Midbrain, the Hypothalamus and the Rostral cortex. These new connections with the Basal Ganglia, an important part of the brain for habit formation, can be further targeted for anti-addictive treatment and preventing relapse. Additionally, rats treated with Ibogaine experienced a significant Positive BOLD response, with significant change in the Cerebellum, Medulla, Hypothalamus, Thalamus and Somatosensory Cortex. A BOLD response in these regions, without activation of the Dopaminergic system due to a decrease in Hypothalamus activity, can also be used to prevent the reward system associated with abused substances. Overall, the Whole-Brain Dose Response shows significant activity between the High dose of Ibogaine when compared to the Vehicle, and very little change with the Low and Medium doses, implying a Non-Monotonic Dose Response with Ibogaine. A High-Dose of Ibogaine has the potential to create connections to the habit-forming parts of the brain, without activating the reward system, which can make it a powerful anti-addictive treatment.

Future Directions

Anti-Addiction Treatments
- Opioid Use Disorder
- Alcohol Use Disorder

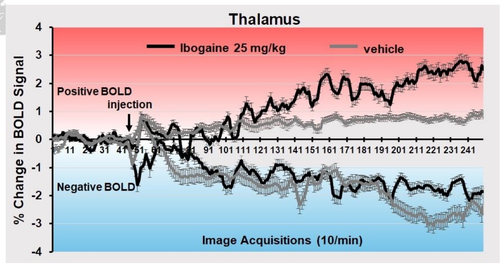
Behavioral Tests
- Conditions Placed Preference Tests (Reward Stimuli)
- Intravenous Self-Administration Tests (Addiction)
- Craving Incubation Tests (Relapse)

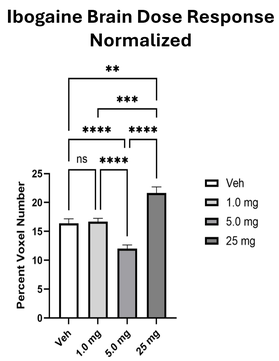
Results

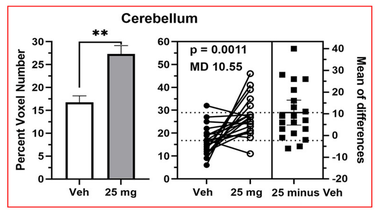
Pharmacological fMRI
- Significant Positive BOLD response, negligible Negative BOLD response
- Positive BOLD response to Ibogaine was greater than VEH Positive BOLD

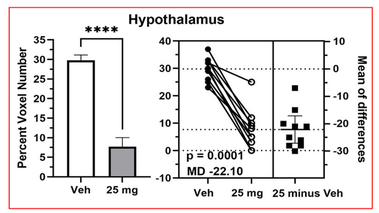
Resting State Functional Connectivity
- Ibogaine increased connectivity between the Ventral Tegmental Area, the Substantia Nigra Complex and the Substantia Nigra Reticularis, all part of the Basal Ganglia
- Ibogaine increases activity in the motor cortex, without activation of the Hypothalamus

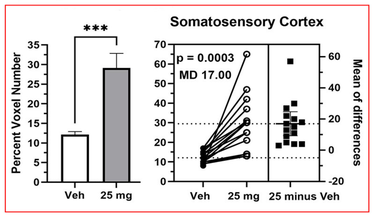
Dose-Response
- Low-Dose decreases connectivity to the Midbrain
- High-Dose engages the Cerebellum

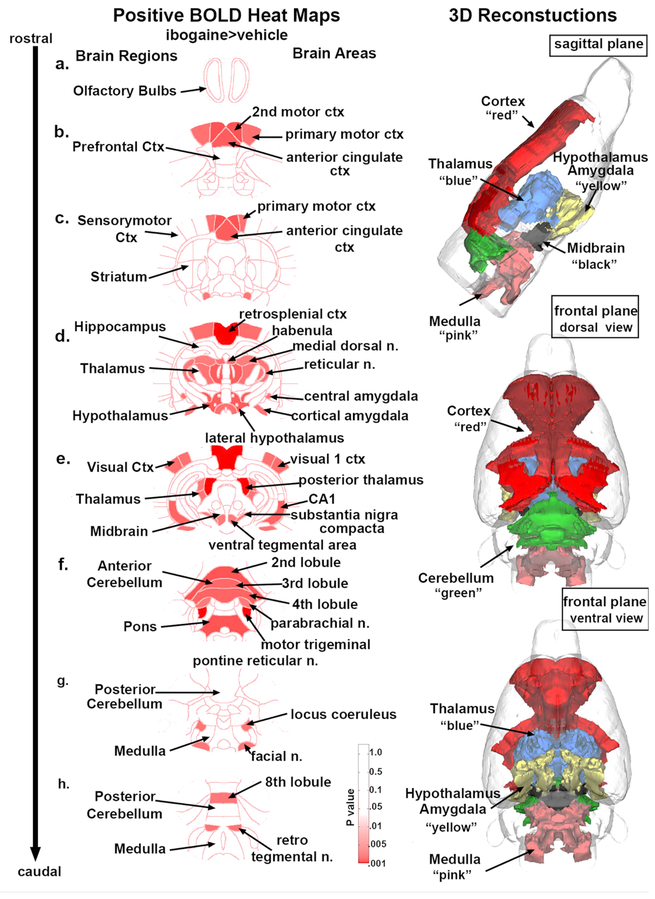


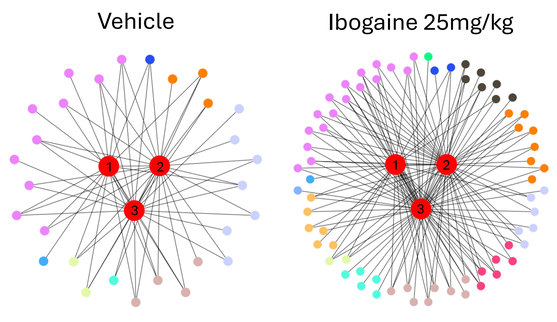






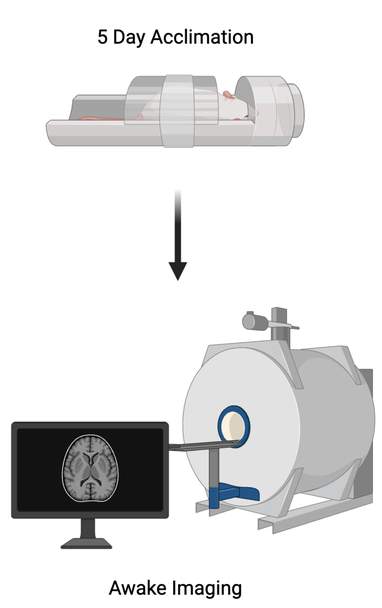






Experimental Methods

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. The rats were first subjected to 1 week 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. Ibogaine was administered 5 minutes into the scan. Both acclimation and scanning was conducted using reverse L/D cycles to maintain the natural circadian rhythms of the rats.



Acknowledgements

Center for Translational Neuro-Imaging

EKAM THE IMAGE OF DRUG DISCOVERY

NIDA Advancing Addiction Science for 50 years