RISE RESEARCH INNOVATION SCHOLARSHIP ENTREPRENEURSHIP

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Dose-Dependent 5-HT2A-Mediated Brain Activity Changes After Psilocybin: BOLD phMRI Study in Rats

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Background

Amidst the War on Drugs in 1971, the United Nations classified psilocybin (PSI) and other psychedelic drugs as Schedule 1 substances. However, in the past decade, there has been a resurgence of scientific interest in PSI. Small clinical trials report promising results in treating MDD, end-of-life distress, PTSD, and alcoholism. Animal studies report that low doses of PSI act through 5HT2a receptors to decrease anxiety and promote prosocial behavior, while higher doses also alter dopaminergic signaling, causing cognitive dysfunction. How does PSI 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 PSI.

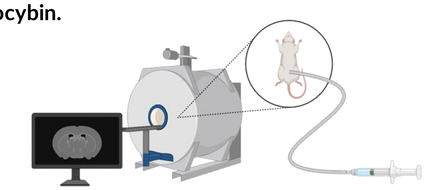
Experimental Design

Subjects & Treatment
- 48 young adult Sprague-Dawley rats (24M, 24F) received IP injections of vehicle or psilocybin (0.03, 0.3, 3.0 mg/kg).

Imaging & Data Collection
- fMRI BOLD signal changes recorded 20 min post-injection.
- Resting-state connectivity data collected ~25 min post-injection.
- Data registered to 3D MRI atlas (173 brain regions) for BOLD fMRI & rsFC analysis.

Experimental Conditions
- Dim red light (10:00–18:00 hrs) to avoid light-dark transitions.
- Blood collected (35 min post-injection) for psilocybin/psilocin assay.
- Injections administered while awake during imaging.

5-HT$_2$A Antagonism
- Ketanserin (2 mg/kg) given 45 min before imaging.
- Rats then imaged for fMRI & rsFC with 3.0 mg/kg psilocybin.

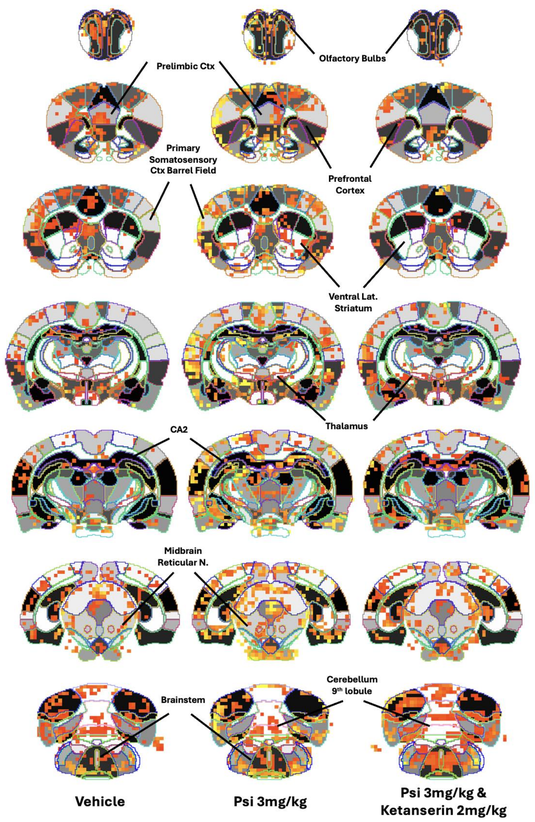


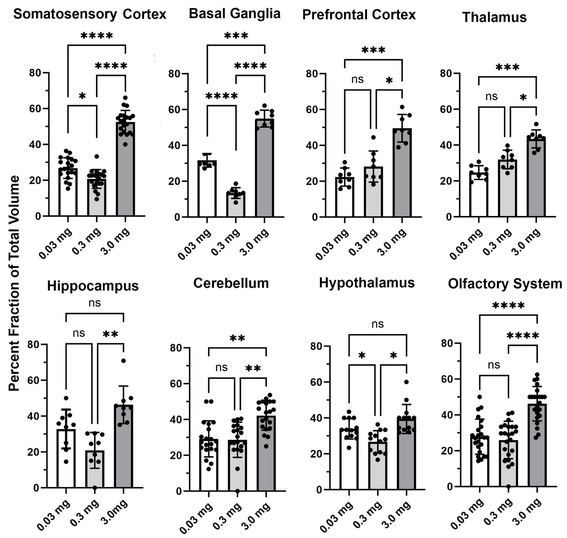
Future Directions

Future research should examine brain and plasma lipidomics to assess endocannabinoid system changes. The cerebellum's role in psilocybin's effects warrants further study in cognition, emotion, and sensory processing. The lab will explore long-term neuroplasticity, synaptic changes, and reward/fear processing, particularly in neurodegenerative diseases like Parkinson's.

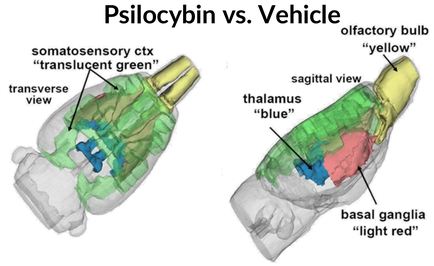
BOLD Pharmacological Functional MRI

2D Positive BOLD Activation Map

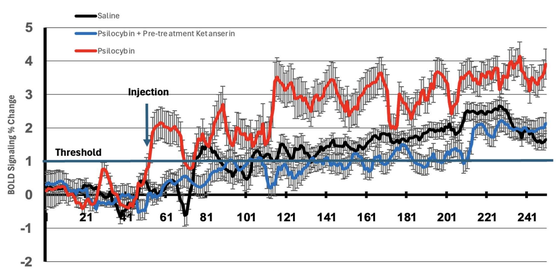




3D Positive BOLD Activation Psilocybin vs. Vehicle

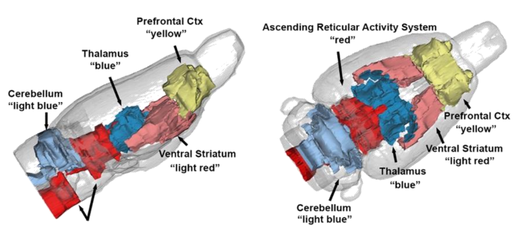


Δ Bold of the Somatosensory Cortex over Time (s)



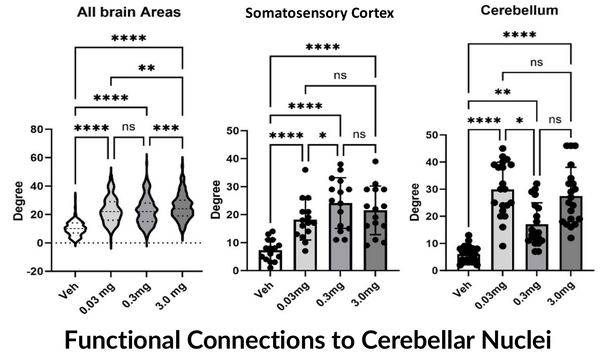
3D Positive BOLD Activation Following 0.3mg/kg Psilocybin

Sex Differences Females>Males

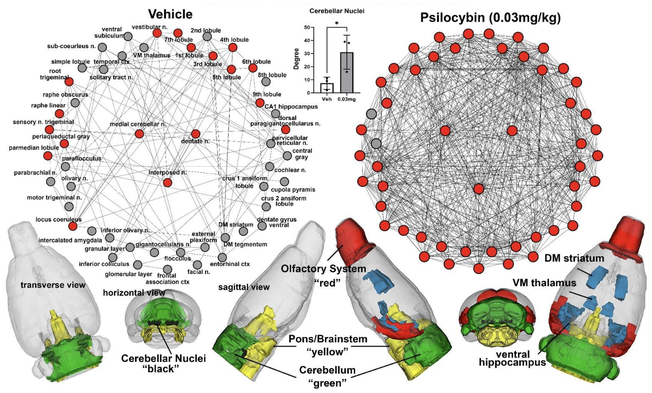


Functional magnetic resonance imaging (fMRI) showed a dose-dependent increase in positive BOLD signaling with psilocybin (PSI), peaking at 4% in the somatosensory cortex and basal ganglia (3.0 mg/kg). A U-shaped response appeared in some areas, with 0.3 mg/kg showing the lowest activation. 33 brain regions were significantly activated, including the olfactory bulb, striatum, anterior cingulate, and thalamus. Ketanserin blocked PSI-induced activation, confirming 5-HT$_2$A involvement. Females exhibited greater activation (0.3 mg/kg) in 45 regions, including the prefrontal cortex, ventral striatum, thalamus, and reticular activating system. Results were visualized via 2D/3D heat maps.

Resting State Functional MRI



Functional Connections to Cerebellar Nuclei



Resting state functional connectivity (rsFC) illustrated a dose-dependent difference in connectivity among 11 major brain regions, represented as violin plots for all 173 brain regions. The average degree of connections increased with each dose: vehicle (Avg Degree: 10.08), 0.03 mg/kg (22.97), 0.3 mg/kg (22.42), and 3.0 mg/kg (25.47). A significant treatment effect was observed with many regions like the olfactory system and somatosensory cortex showing greater connections than the vehicle but not among themselves. Notably, the medulla and cerebellum displayed a U-shaped response, with the 0.3 mg/kg dose yielding the lowest connections. The cerebellar nuclei exhibited significant increases in connections with low-dose PSI treatment, expanding to various brain areas, as detailed in a 3D reconstruction.

Acknowledgments

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Advancing Addiction Science

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