RISE RESEARCH INNOVATION SCHOLARSHIP ENTREPRENEURSHIP

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Exploring Psilocybin as a Treatment for Repetitive Mild Traumatic Brain Injuries

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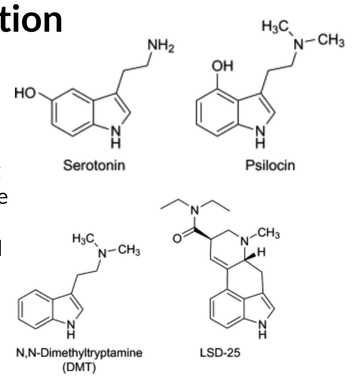
EKAM THE IMAGE OF DRUG DISCOVERY

Background, Motivation, & Goals

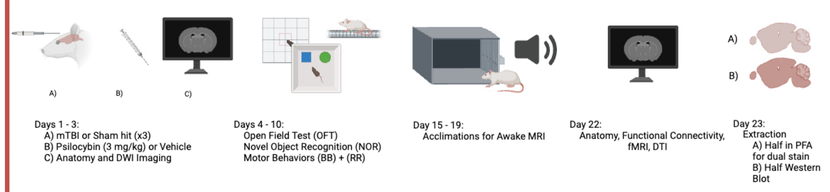
Introduction

Repetitive Mild Traumatic Brain Injuries (rmTBI), commonly known as concussions, pose a significant risk factor for neurodegenerative diseases later in life. Research on **serotonin 2A agonists**, including psilocybin, suggests their potential to mitigate cognitive impairments and promote synaptogenesis—the formation of new neural connections. Our study investigates the neuroprotective effects of serotonin 2A agonists in the context of rmTBI and subsequent neurodegeneration.



Process and Methods

Approach



Subjects

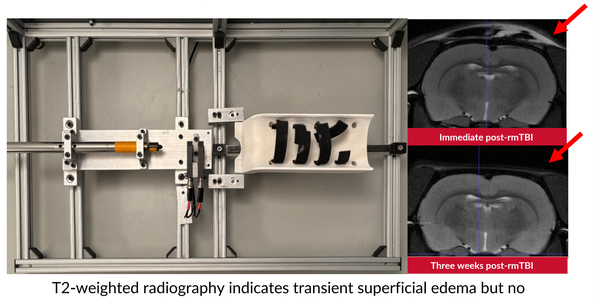
- Adult Wistar rats (*N*=24, 100% female)
- Three experimental groups: Sham rmTBI + Vehicle (*n*=8), rmTBI + Vehicle (*n*=8), rmTBI + Psilocybin (*n*=8).

Experimental Design

- Three consecutive days of mild traumatic brain injury with psilocybin or vehicle treatment via aqueous IP injection after 20 minutes
- Post-treatment: blood sampling and 7T *in vivo* MRI imaging, followed by cognitive and motor assessments
- Acclimated before engaging in the awake neuroimaging session
- Concludes with brain extraction for immunohistochemistry and Western Blot

Momentum Exchange Model of mTBI

Closed-head injury is induced by rapid acceleration of the head in awake, active-phase, buprenorphine-treated rats to simulate sport-related concussion with maximal translational value.

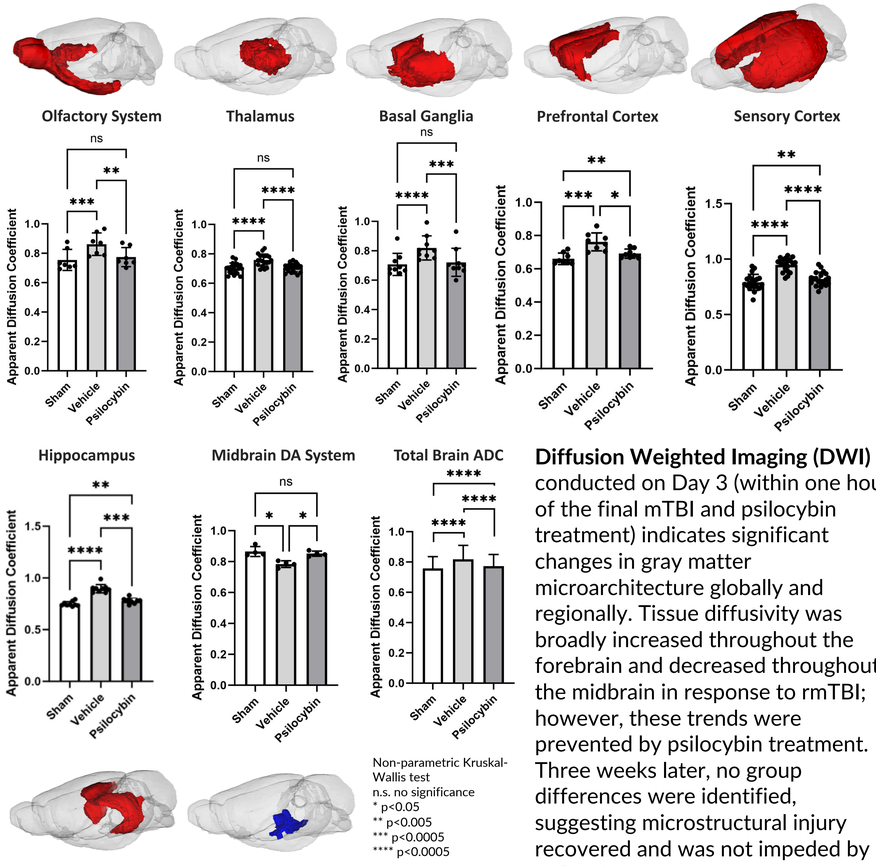


T2-weighted radiography indicates transient superficial edema but no neuroanatomical injury or skull fracture following rmTBI.

Findings

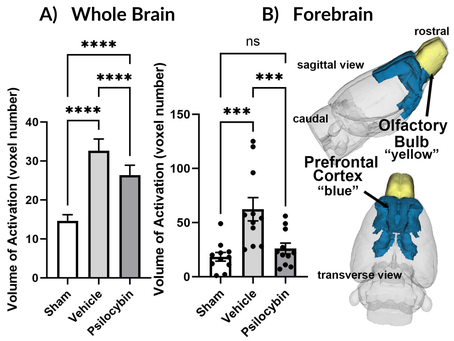
Imaging

Acute Administration of Psilocybin Prevents Early Peak in Neuroinflammation Induced by rmTBI



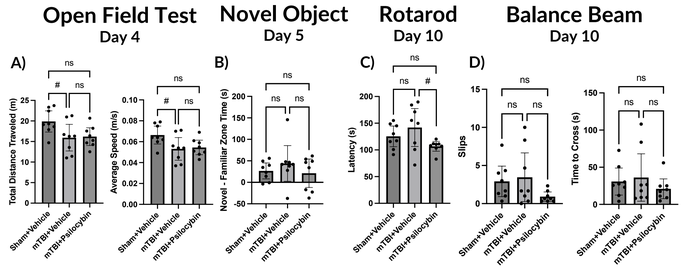
Diffusion Weighted Imaging (DWI) conducted on Day 3 (within one hour of the final mTBI and psilocybin treatment) indicates significant changes in gray matter microarchitecture globally and regionally. Tissue diffusivity was broadly increased throughout the forebrain and decreased throughout the midbrain in response to rmTBI; however, these trends were prevented by psilocybin treatment. Three weeks later, no group differences were identified, suggesting microstructural injury recovered and was not impeded by psilocybin.

Psilocybin Treatment Limits Lasting Alterations to Neurovascular Coupling



Functional Magnetic Resonance Imaging (fMRI) conducted on Day 22 (three weeks post-rmTBI) indicates a lasting hyperactive Blood Oxygen Level Dependent (BOLD) signal response to 5% CO_2 challenge is induced by rmTBI. This functional alteration is limited globally by psilocybin treatment **(A)** and prevented entirely in prefrontal cortex and olfactory system **(B)**.

Behavioral Assays



Consistent with prior reports of the momentum exchange model of mild head injury, few behavioral effects were observed in the first week post-rmTBI. Open Field testing on Day 4 indicated a trend toward significantly reduced locomotor exploration in both injury conditions **(A)**. Rotarod testing on Day 10 indicated a trend toward significantly reduced latency in the psilocybin condition **(C)**, however beam walk results on the same day indicate this trend is likely not indicative of motor skill impairment **(D)**.

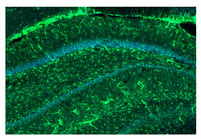
One-Way ANOVA: n.s. no significance; # p ≤ 0.057

Discussion

Our study suggests that psilocybin, a promising serotonin 2A agonist, may offer short-term and long-term benefits for brain health following repetitive mild traumatic brain injuries (rmTBI), aligning with the known role of serotonin 2A receptors in promoting synaptic plasticity and Brain Derived Neurotrophic Factor (BDNF)-linked neurogenesis pathways. Further analysis is needed to elucidate the mechanisms underlying the observed changes in tissue diffusivity and neurovascular coupling, and future research must explore prevention of long-term neurodegeneration. Overall, our findings contribute to the growing evidence supporting the therapeutic potential of psychedelics, particularly in the context of brain injuries, opening new avenues for treatment.

Next Steps

- **Neuroimaging:** add remaining subjects and analyze functional connectivity scans
- **Spectroscopy:** analyze blood plasma for psilocin concentration and lipid biomarkers of concussion
- **Tissue Analysis**: immunohistochemistry and Western Blotting for GFAP (astrocytes) and IBA1 (microglia) proteins
- Manuscript writing and subsequent publication



GFAP⁺ astrocytes in the rat hippocampus (Brengel et al., *in prep.*)

Acknowledgments

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