RISE RESEARCH INNOVATION SCHOLARSHIP ENTREPRENEURSHIP

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Evaluating Psilocybin as a Treatment for rmTBI-Induced Neuroinflammation Using Glial Histology

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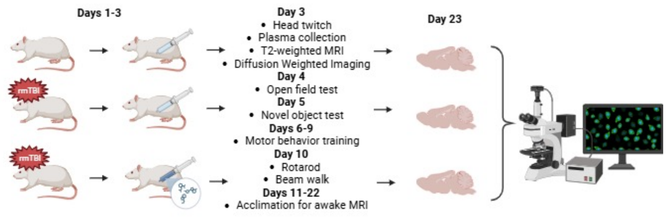
EKAM
THE IMAGE OF DRUG DISCOVERY

Introduction

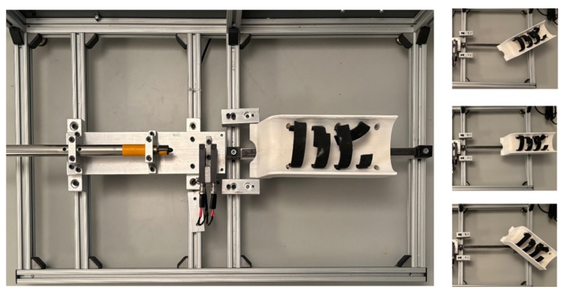
Repetitive mild traumatic brain injury (rmTBI) is a highly prevalent risk factor for neurodegenerative disease onset later in life. These injuries, commonly known as concussions, account for approximately 80% of all TBI cases globally per year. Glial cells have garnered interest for their role in the brain's trauma response, as they secrete pro-inflammatory cytokines that are closely associated with neurological disease. Our study quantifies astrocytes and microglia, two key markers of the neuroinflammatory response, to explore the potential of psilocybin, a naturally occurring psychedelic and serotonin agonist, as a treatment for rmTBI due to its neuroplastic action and anti-inflammatory effects.

Experimental Design



Momentum Exchange Model

The momentum exchange method ranks highly among preclinical rmTBI models in translational value for its ability to generate tightly regulated, ethologically valid acceleration without skull fracture or surgical procedure. The apparatus features a pneumatic impactor, sensors to verify velocity, and a track along which the platform accelerates after impact for longitudinal use with fully awake rats.



Proteomics and Histology

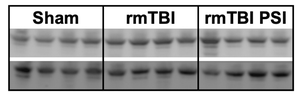
Collaborators at Delaware State University used Western Blots to quantify protein concentrations across the prefrontal cortex (PFC). Follow-up histology was conducted in-house for cell quantification and morphological analysis in the substantia nigra (SN) and hippocampus (HPC).

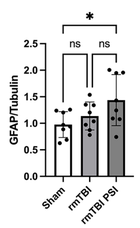
Astrocytes	Maintenance of synapses and BBB integrity
Microglia	Neural tissue repair and waste clearance
pTDP-43	Nucleus protein phosphorylated in pathology

Region-Specific Changes in Intensity and Morphology of Neuroinflammatory Biomarkers

Astrocytes

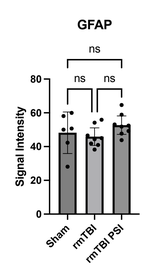
Prefrontal Cortex



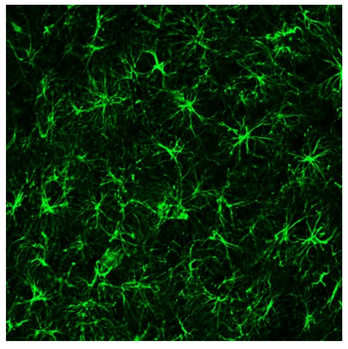


Western Blot signal intensity of GFAP in the prefrontal cortex is increased by psilocybin treatment (p = 0.0378).

Substantia Nigra

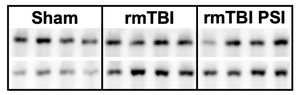


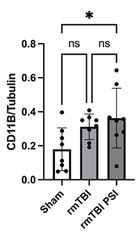
Histological signal intensity of GFAP in the substantia nigra is not affected by repetitive mTBI or psilocybin treatment (p = 0.2589).



Microglia

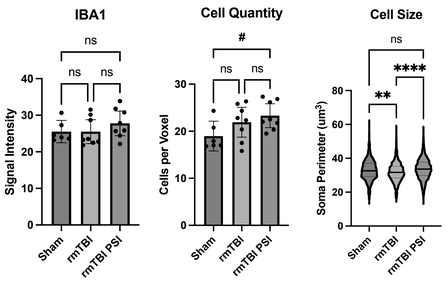
Prefrontal Cortex

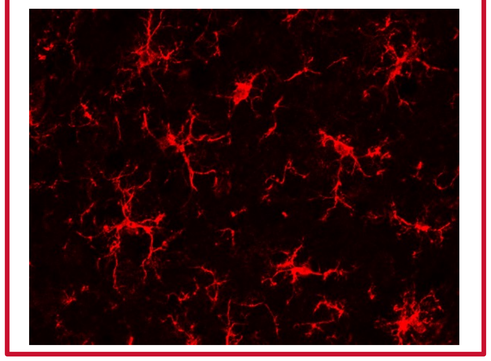




Above: CD11B intensity in the PFC is increased by psilocybin treatment (p = 0.0378). *Below:* A trend toward increased microgliosis is observed in rmTBI-PSI (p = 0.0766). Soma size is reduced in rmTBI-VEH (p = 0.0294).

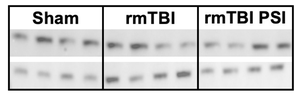
Substantia Nigra

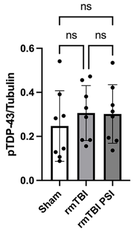




TDP-43

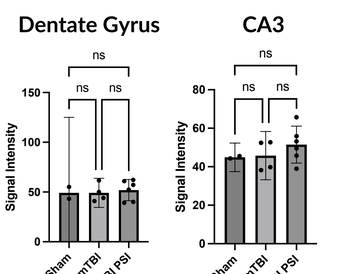
Prefrontal Cortex



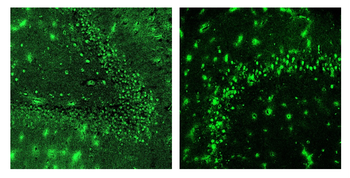


Neither TDP-43 nor its phosphorylated conformation display altered signal intensity in the prefrontal cortex (p > 0.05).

Hippocampus



Preliminary analysis does not display altered signal intensity in the substantia nigra for nuclear and cytoplasmic phosphorylated TDP-43 (p = 0.0378).



Discussion

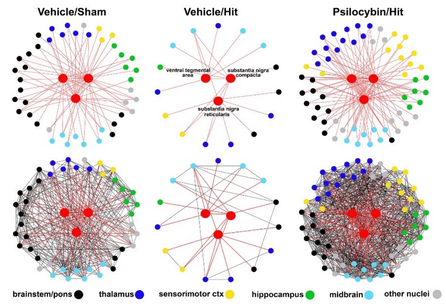
•**Proteomics and Histology**: Taken together, findings from Western Blotting and immunohistochemical staining suggest a neuroprotective role of increased gliosis following psilocybin treatment.

•**Behavior:** There were no significant differences in groups in the Beam Walk, Rotarod, or Open Field. Short-term memory was also not significantly affected in Novel Object Recognition.

•**Diffusion-Weighted Imaging:** A transient spike in global vasogenic edema was observed following repetitive mild traumatic brain injury. This surge was largely prevented by psilocybin treatment in the olfactory system, thalamus, basal ganglia, prefrontal cortex, sensory cortex, hippocampus, and midbrain dopaminergic system.

•**Vascular Responsivity:** Lasting hyperreactivity to CO_2 challenge during functional MRI was observed three weeks post-rmTBI. This responsivity was returned to control levels in the olfactory system and prefrontal cortex.

•**Functional Connectivity:** Psilocybin was found to prevent extreme loss of global functional connectivity and even restored connectivity beyond control levels. Illustrated below are changes in connectivity of the midbrain dopaminergic system.



Future Directions

Histology
- Western Blot signal intensity in the prefrontal cortex will be corroborated with astrocyte and microglia histology
- Further analysis of phosphorylated TDP-43 histology in the hippocampus and prefrontal cortex

Future studies

The present study was conducted in adult female Wistar rats (n = 24) treated within 10 minutes of each mild head injury.
- Study various age populations, including adolescent and older rats
- Test different times at which treatment is administered post-injury
- Evaluate potential differences in neurological activity in males and females

Acknowledgements

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