# Sensitive period of plasticity emerges after delayed psilocybin treatment for repetitive mild head injury: A preclinical MRI study

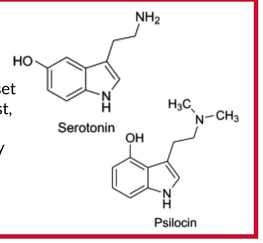
Eric Brengel, MS[1,2], Ashwath Maheswari, MS[1,3], Anna Moore[1], Eva Bennet[1], Muhammad Abeer, MS[4], Richard Ortiz, PhD[5], Praveen Kulkarni, PhD[1,2], Michael Gitcho, PhD[4] & Craig Ferris, PhD[1,2,3]

[1]Center for Translational Neuroimaging, Northeastern University, Boston, MA; [2]Dept Psychology, Northeastern University, Boston, MA; [3]Dept Pharmaceutical Sciences, Northeastern University, Boston, MA; [4]Dept Biological Sciences, Delaware State University, Dover, DE; [5]Dept Psychology, Northern Illinois University, DeKalb, IL

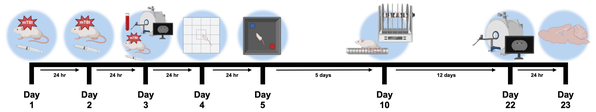
Center for Translational Neuro-Imaging

## Introduction

**Repetitive Mild Traumatic Brain Injury (rmTBI),** poses a significant risk factor for neurodegenerative disease onset later in life. Psilocybin (PSI), a psychedelic 5-HT$_{2A}$ agonist, has recently garnered interest as a robust promoter of neuroplasticity with synaptogenic and anti-inflammatory effects. Our study is among the first to investigate the neuroprotective effects of PSI as a treatment for rmTBI using a multimodal preclinical approach.




## Acute Treatment Experimental Design




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Animal Procedures | • Hit<br>• Treatment | • Hit<br>• Treatment | • Hit<br>• Treatment | | | • Motor behavior training | | • Acclimation for awake fMRI | |
| Behavior | • Head twitch | • Head twitch | • Head twitch | • Open Field | • Novel Object | | • Rotarod<br>• Beam Walk | | |
| Sample Collection | | | • Plasma for lipidomics | | | | | | • Western Blot<br>• Immunohistochemistry |
| Neuroimaging | | | • T2-weighted MRI<br>• Diffusion Weighted Imaging | | | | | | • T2-weighted MRI<br>• Resting-state Functional Connectivity<br>• $CO_2$ Challenge fMRI<br>• Diffusion Weighted Imaging |

The main analysis was conducted with middle-aged (9-month) female Wistar rats (*N*=24) in three experimental groups: 1) sham impact with vehicle, 2) rmTBI with vehicle, and 3) rmTBI with PSI treatment. A pilot cohort of older adult (18-month) female rats (*N*=12) was studied for investigation at an additional period of vulnerability.

## Momentum Exchange Model

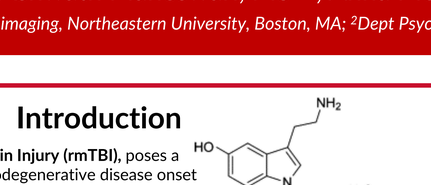
The momentum exchange method ranks highly among preclinical mTBI models in translational value for its ability to generate tightly regulated, ecologically valid closed-head injury in awake, active-phase rats. Upon impact (7.4 m/s), the cradle accelerates backward along its track.



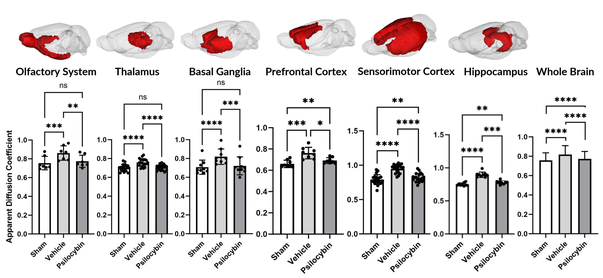




Radiography indicates no skull fracture or gross anatomical damage. Transient superficial edema of the tissue overlying the skull at the site of impact is shown on the third day of rmTBI.

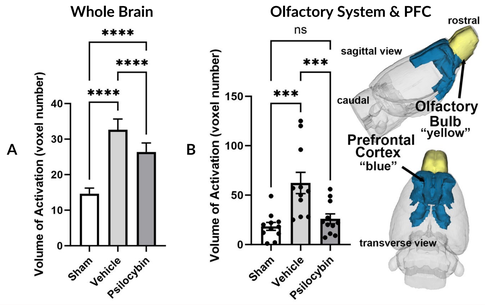


## Acute Treatment Prevents Early Peak in Vasogenic Edema Induced by rmTBI




**Diffusion Weighted Imaging (DWI)** conducted on Day 3 indicates significant changes in gray matter microarchitecture globally and regionally. Tissue diffusivity was broadly increased throughout the forebrain, indicating transient vasogenic edema in response to rmTBI. These trends were prevented or mitigated by PSI treatment. Three weeks later, no group differences were identified, suggesting microstructural injury recovered and was not impeded by psilocybin. Non-parametric Kruskal-Wallis test: n.s. no significance; * p<0.05; ** p<0.005; *** p<0.0005; **** p<0.00005

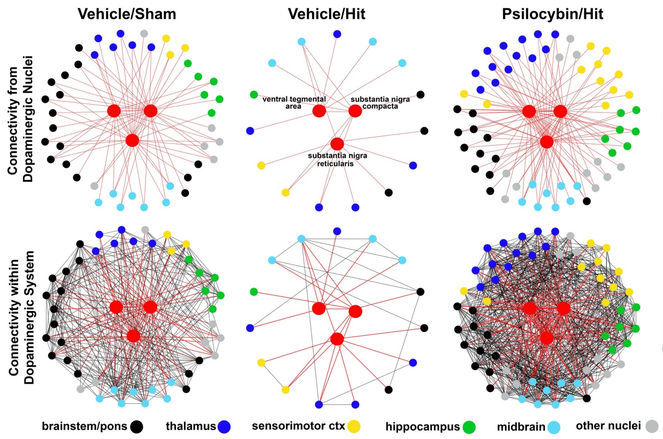
## Acute Treatment Limits Lasting Cerebrovascular Hyperreactivity

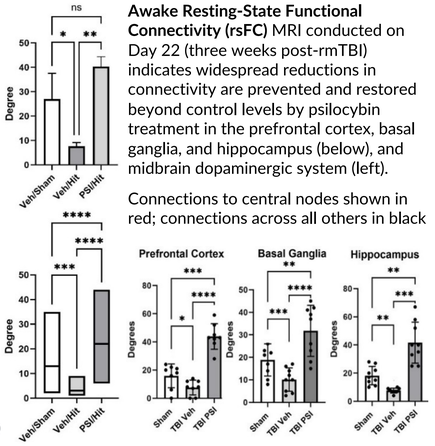



**Functional Magnetic Resonance Imaging (fMRI)** was conducted in awake rats on Day 22 (three weeks post-rmTBI) with a hypercapnic challenge. As a measure of cerebrovascular reactivity, blood-oxygen-level-dependent (BOLD) signal changes from baseline were recorded during exposure to 5% $CO_2$ inhalation. Significant increases in the volume of positive BOLD activation throughout the brain indicates a compensatory increase in the cerebrovascular reactivity of untreated rmTBI rats relative to untreated sham rats. Critically, this lasting functional alteration is limited globally in psilocybin-treated rmTBI rats **(A)** and prevented entirely in the olfactory system and prefrontal cortex of psilocybin-treated rmTBI rats **(B)**.

Non-parametric Kruskal-Wallis test: n.s. no significance; * p<0.05; ** p<0.005; *** p<0.0005; **** p<0.00005

## Acute Treatment Reverses Lasting Loss of Functional Connectivity

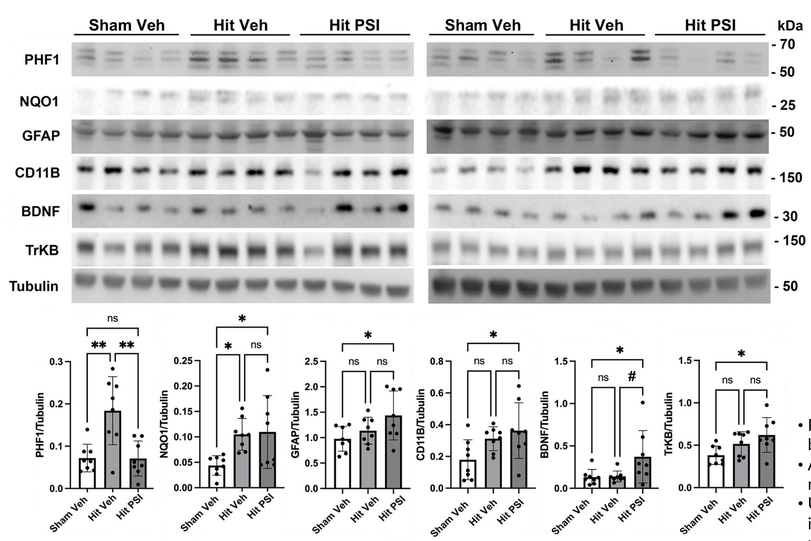


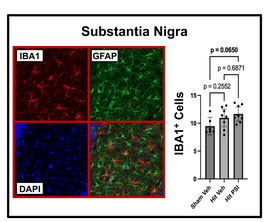



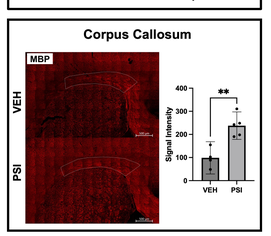

**Awake Resting-State Functional Connectivity (rsFC)** MRI conducted on Day 22 (three weeks post-rmTBI) indicates widespread reductions in connectivity are prevented and restored beyond control levels by psilocybin treatment in the prefrontal cortex, basal ganglia, and hippocampus (below), and midbrain dopaminergic system (left).

Connections to central nodes shown in red; connections across all others in black

## Acute Treatment Limits Tau Hyperphosphorylation, Promotes Gliosis, and Upregulates BDNF Expression

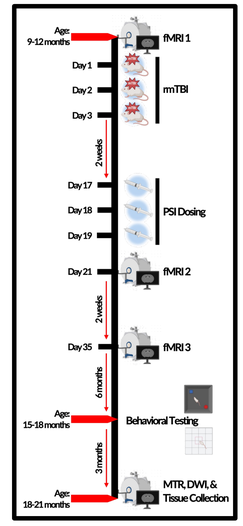


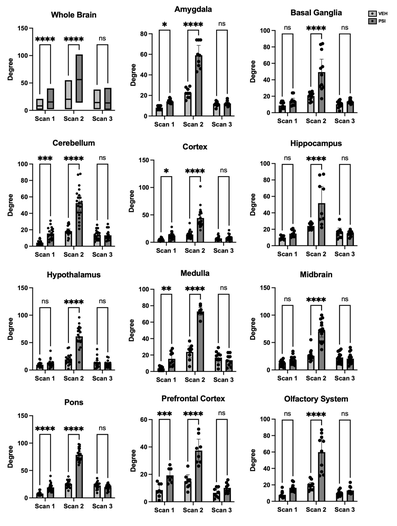



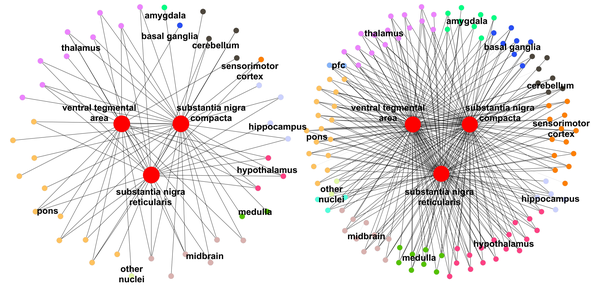

- Reduction of phosphorylated tau buildup could reduce long-term deficit
- Astrocytosis, microgliosis, and myelination are augmented by PSI
- Upregulated BDNF-TrkB expression indicates a potential therapeutic mechanism.

## Delayed Treatment Induces Period of Global Hyperconnectivity




## Midbrain Dopaminergic Connectivity




Middle-aged female Sprague-Dawley rats (*N*=15) were tracked longitudinally to assess delayed treatment efficacy. Global hyperconnectivity was observed in rmTBI-PSI rats at Scan 2 that largely returned to baseline levels at Scan 3 ($p < .0001$), suggesting the emergence of a sensitive period of neuroplasticity after PSI treatment.

## Discussion

These findings establish a body of preclinical evidence supporting the therapeutic efficacy of PSI treatment to improve short-term and long-term brain health following rmTBI. Importantly, this investigation was conducted with a mild head injury model that reflects the human condition, without skull fracture or the confound of anesthesia, in an understudied female population at multiple timepoints in adulthood and under multiple dosing schema.

**Future Directions**

- Elucidate mechanisms of PSI therapeutic action with agonists and antagonists for 5-HT$_{2A}$ and TrkB receptor pathways
- Conduct behavioral assays of executive function (minimal change was observed with the current behavioral battery)
- Characterize functional role of the PSI-augmented glial response
- Replicate with males and examine sex differences

## Acknowledgments

- **Psilocybin:** National Institute on Drug Abuse
- **Project Funding:** Ekam Imaging

**I am on the job market! PhD expected Spring 2027**

✉ **brengel.e@northeastern.edu**

Scan for more from Ekam Imaging

EKAM