

Baseline Neural Effects of Psilocybin in the Healthy Brain

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Introduction

Psilocybin, a naturally occurring psychedelic, has been studied for its potential therapeutic effects in models of repetitive mild traumatic brain injury (rmTBI). Recent findings show that psilocybin is associated with decreased injury-related edema, as well as boosted functional connectivity between certain brain regions following rmTBI. This study aims to supplement existing research by investigating the baseline effect of psilocybin on the healthy brain. By examining the same parameters in a non-injured brain, this research will help to establish a reference framework for interpreting psilocybin-induced neural changes, and advance our understanding of how psilocybin influences brain function under non-pathological conditions.

PSI induces lasting increases in positive BOLD activation during CO₂ Challenge

Functional MRI with Hypercapnic Challenge

Awake, acclimated rats were scanned for 15 min with a 5-min off-on-off exposure paradigm to 5% CO₂ inhalation. This vasoactive stimulus is a clinically relevant assessment of cerebrovascular reactivity.

Wilcoxon signed-rank tests indicate a significant global increase in positive BOLD activation during CO₂ challenge ($W = 7215, p < 0.0001, r_c = 0.51$), driven by localized increases.

- PFC ($W = 28, p = 0.016, r_c = 0.62$)
- Cortex ($W = 97, p = 0.033, r_c = 0.51$)
- Thalamus ($W = 73, p = 0.020, r_c = 0.38$)
- Midbrain ($W = 45, p = 0.004, r_c = 0.58$)
- Lower Brainstem ($W = 178, p < 0.0001, r_c = 0.85$)
- Cerebellum ($W = 190, p < 0.0001, r_c = 1$).

No significant changes seen in Rotarod assay performance

Unpaired t-test with Welch's correction indicates no significant difference in performance on the Rotarod assay (latency to dismount averaged across valid trials on test day) was observed between rats treated with PSI and VEH ($t_{10.72} = 0.32, p = 0.754$). This is expected and consistent with prior our finding that there was no change in Rotarod dismount latency due to rmTBI or PSI treatment (see figure insert).

Discussion

Cerebrovascular Reactivity (CO₂ Challenge):

- Significant global and regional increases with PSI treatment
- Consistent with prior findings in head-injured rats
- PSI may increase reactivity in healthy brain and stabilize hyperreactivity in the injured brain

Functional Connectivity:

- Limited increase 3 weeks post treatment
- Suggests previous finding of lasting hyperconnectivity is a specific therapeutic phenotype in head-injured rats

Rotarod:

- No significant difference between PSI and vehicle
- Confirms PSI does not affect baseline motor function

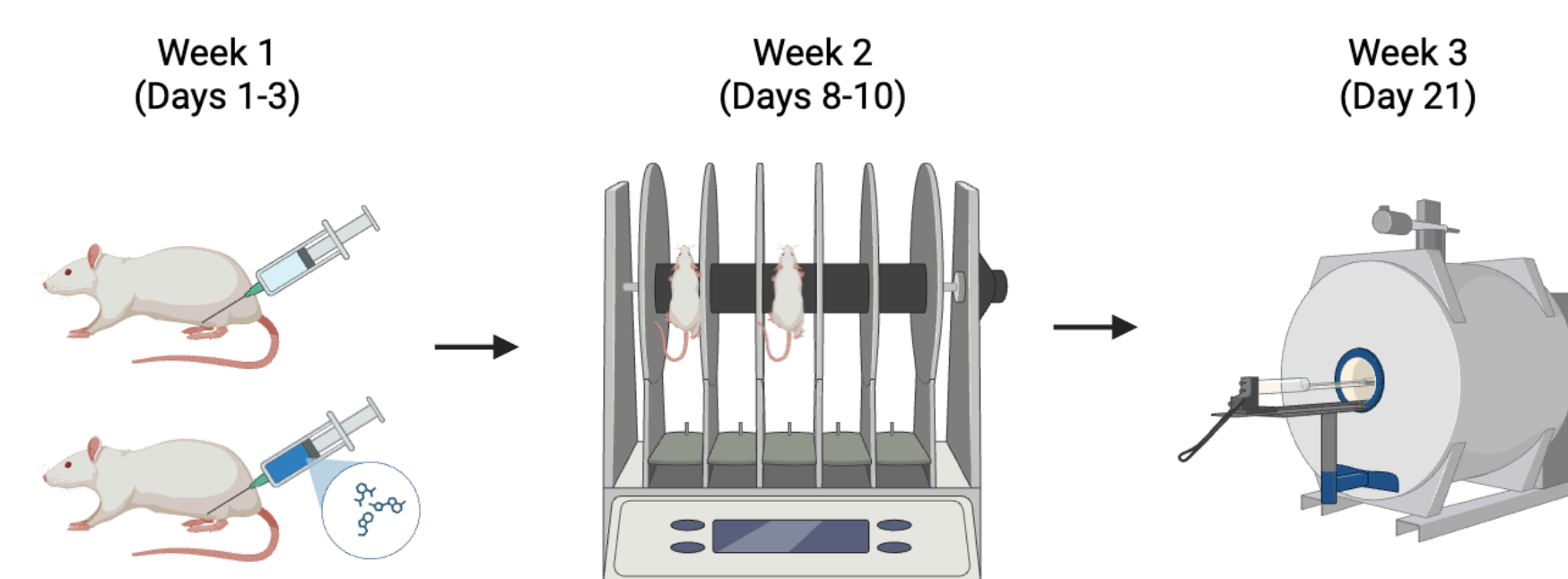
Limitations

- Differences in age and strain → limits direct comparison to prior head injury studies
- Single timepoint at 3 weeks, may miss dynamic changes

Future Directions

- Directly compare healthy vs. head-injured subjects within the same study
- Include longitudinal timepoints
- Investigate underlying mechanisms of PSI-induced network changes

Experimental Design



Psilocybin Dosing

- 3 mg/kg PSI in saline (or vehicle only) via IP
- 1 dose per day for three days
- Head Twitch Response recorded for 10 min

Rotarod Assay

- Test of motor coordination and endurance on an accelerating, rotating rod
- Procedural control for comparison to rmTBI study

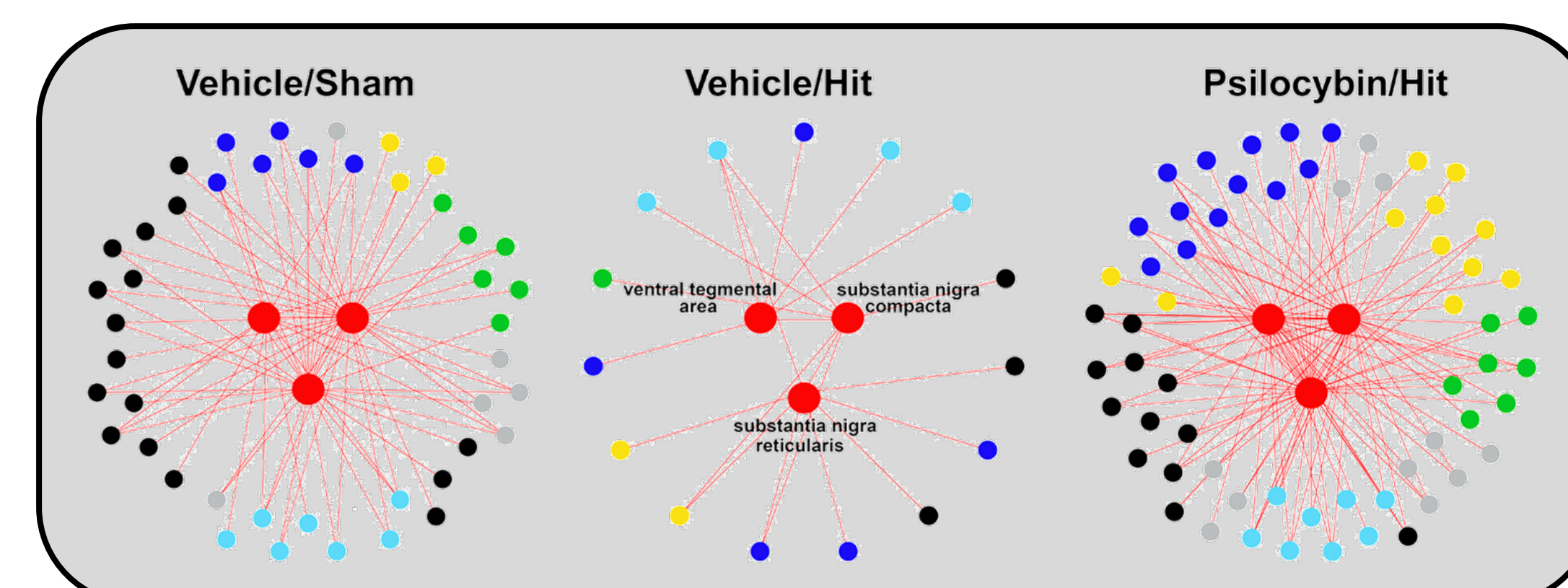
Magnetic Resonance Imaging (MRI)

- Awake fMRI with CO₂ challenge assay
- Awake resting-state Functional Connectivity

PSI induces a limited long-term increase in global connectivity, indicating specificity of treatment for head injury

Baseline

With PSI



Resting-State Functional Connectivity

Awake, acclimated rats were scanned for 15 min to measure natural fluctuations in BOLD signal, with correlation analyses revealing functionally connected brain regions. While PSI has been shown to increase connectivity in head-injured rats (a therapeutic effect), this long-term change is not observed in healthy rats exposed to PSI.

Acknowledgments

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