Chronic non-psychedelic psilocybin therapy promotes visual rehabilitation in mice post-occipital stroke

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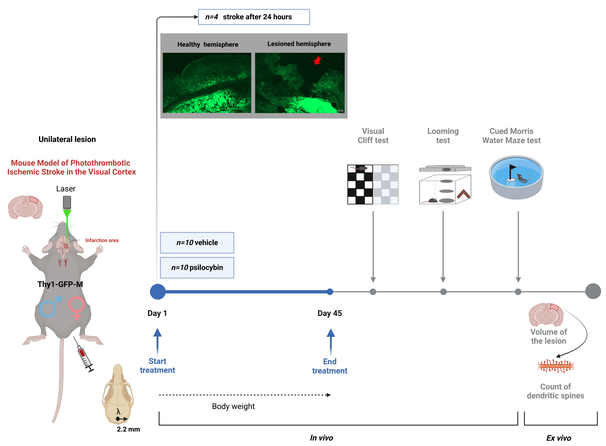
INTRODUCTION

Stroke is one of the leading causes of mortality and long-term disability worldwide, with profound impact on individuals and healthcare systems. Among the different types of strokes, occipital stroke is particularly debilitating, as it directly affects the brain's visual processing centers, often leading to significant visual and functional deficits *(Kerkhoff, 2000)*. Occipital strokes are usually unilateral, causing damage to one hemisphere of the visual cortex, with severe impairments in visual perception and processing. As a result, patients may experience a substantial decline in their quality of life. Currently, there are no effective treatments to restore visual function following an occipital stroke, highlighting an urgent need for innovative therapeutic approaches. Emerging research has pointed to the potential of psychedelics, such as psylocibin, to induce neuroplasticity and promote neurogenesis *(Ly et al., 2018)*. These mechanisms suggest that psychedelics, known for inducing visual hallucinations, may have a particular affinity for visual pathways. Consequently, we hypothesized that psilocybin may stimulate visual pathway restoration following occipital stroke, thereby potentially opening new avenues for improving patient outcomes and reducing long-term disability.

METHODS

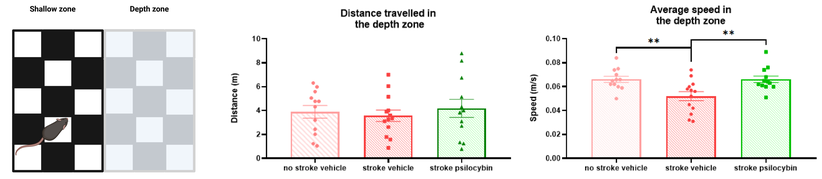
This study investigates the effects of a chronic treatment (45 days) with a low non-psychedelic dose of psilocybin (0.05 mg/Kg) on visual recovery in adult (2-3-month-old) mice subjected to photothrombotic monolateral stroke *(Cambiaghi et al., 2022)* at the visual cortex level. Visual abilities were evaluated after 45 days of psilocybin post- stroke treatment using the Visual Cliff test, the Looming test, and the Cued Morris Water Maze test.



RESULTS

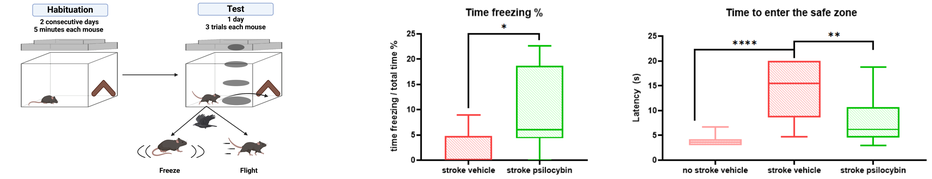
VISUAL CLIFF TEST

Psilocybin treatment restores speed in the depth zone to control levels



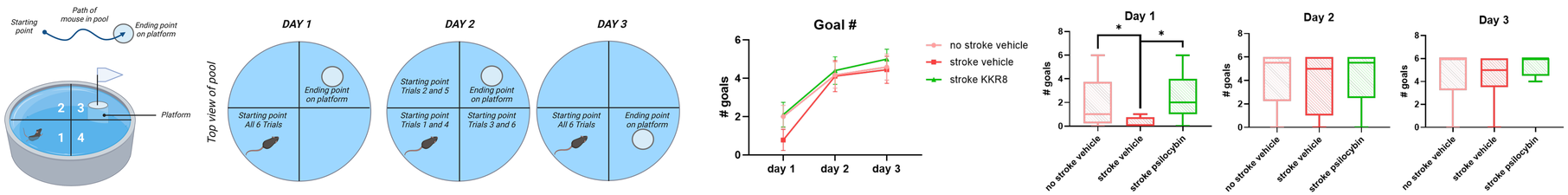
LOOMING VISUAL STIMULI TEST

Psilocybin decreases the time to enter the safe zone to control levels

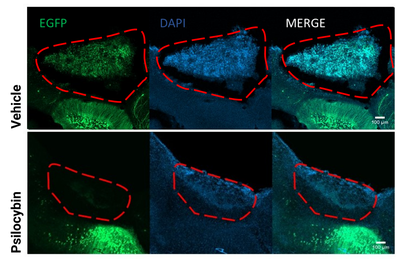


CUED MORRIS WATER MAZE TEST

Psilocybin-treated mice reach the platform more times than vehicle-treated mice on day 1 of the test

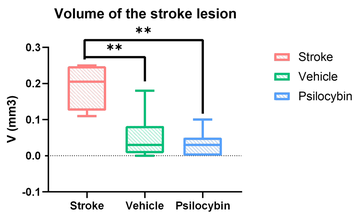


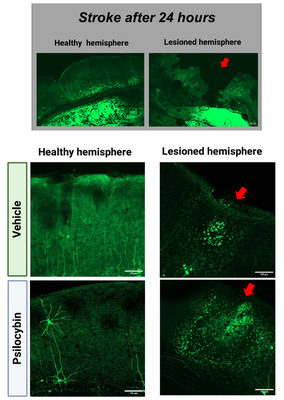
Volume of the lesion after 45 days of treatment



Images were acquired using a ZEISS LSM 800 Confocal Laser Scanning Microscope (Carl Zeiss, Jena, Germany) equipped with a Zeiss 5x zoom 1.0x

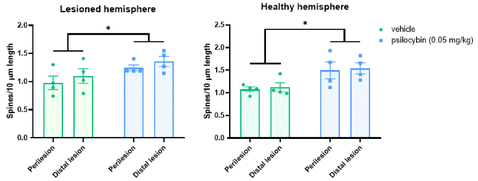
After 45 days both vehicle- and psilocybin-treated animals show reduced volume of lesion compared to 24 hours post-stroke.

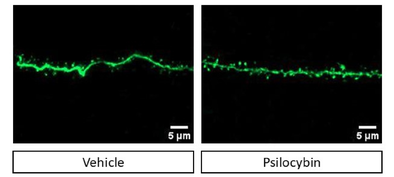




Dendritic spines after 45 days of treatment

Psilocybin induces an increasing in spine density in the perilesion and distal area in both lesioned and healthy emispheres.





Images were acquired using a ZEISS LSM 800 Confocal Laser Scanning Microscope (Carl Zeiss, Jena, Germany) equipped with a Zeiss 63x/1.0– Plan-Apochromat oil objective using the ZEN Blue acquisition software.

CONCLUSION

Overall, these preliminary experiments suggest that a 45-day treatment with 0.05 mg/kg psilocybin, administered 24 hours after inducing a photothrombotic visual cortex stroke in mice, is well tolerated. The treatment appears to improve tasks of visual performance to levels comparable to non-stroke mice and enhances dendritic spines in both the peri-lesional and distal regions of the injury.

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