PSYCHEDELIC-INDUCED NEUROPLASTICITY: DOI AND PSILOCYBIN SHOW PROMISE IN ALLEVIATING COGNITIVE DEFICITS AND STEREOTYPIC BEHAVIORS

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PRECLINICAL RESEARCH

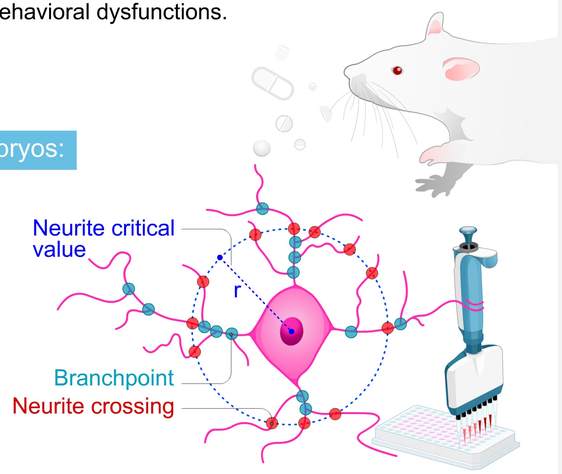
Background / Objective

- **Cognitive deficits** and **repetitive behaviors** are hallmark symptoms of **Alzheimer's disease** (AD), linked to **disrupted synaptic connections** and **impaired neuronal plasticity**.
  Psychedelics, acting as "psychoplastogens," show potential to promote neuronal plasticity, offering a novel therapeutic approach.
- The objective of the present work was to investigate the ability of Psychedelics (for example DOI and Psilocybin) to induce neurite outgrowth and ameliorate cognitive and behavioral dysfunctions.

Methods

Primary neuronal cultures from the cortex of rat embryos:

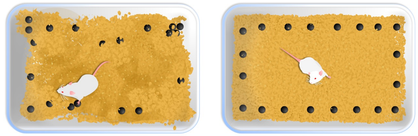
- Assessment of **DOI** and **Psilocin** (the primary metabolite of Psilocybin) effects on **neurite outgrowth**,
- evaluating **parameters** such as primary **neurite number**, total **neurite length**, **branch points**, and **critical neurite value** (radius "r")



Mouse behavioral models:

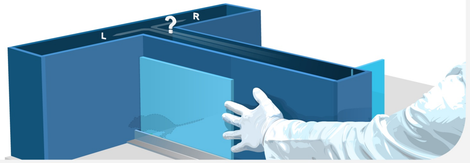
- Marble Burying Task:

  Assessed the effects of **DOI** and **Psilocybin** on repetitive and stereotypic behaviors, measured by the change in frenetic **marble burying** behavior.

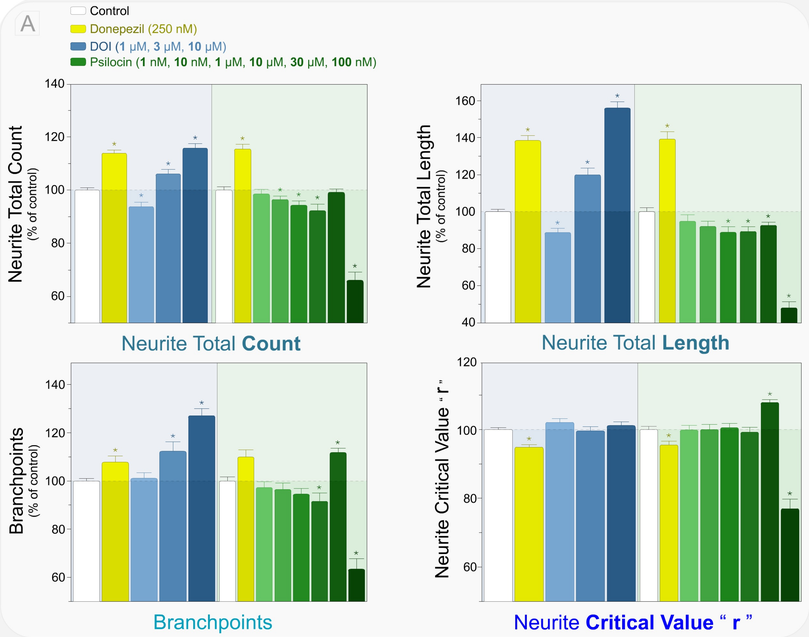


- Scopolamine-Induced Cognitive Deficit model:

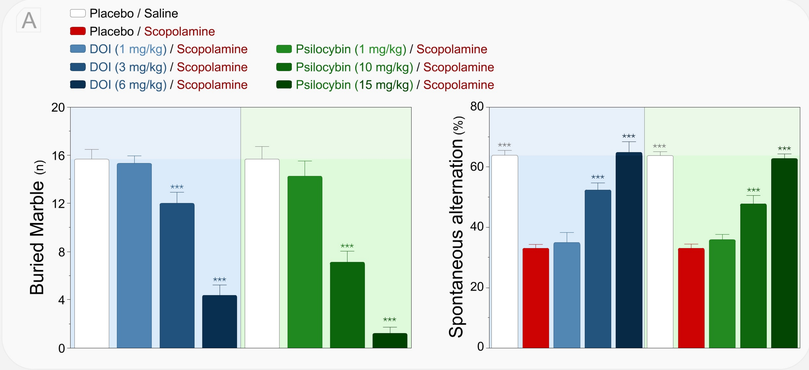
  Evaluated the effects of **DOI** and **Psilocybin** on cognitive deficits, focusing on changes in the reduced spontaneous alternation behavior of scopolamine-treated mice in the **T-maze**.



Results



DOI increased neurite number, total length, and branch points dose-dependently.
Psilocin increased branch points and the neurite critical radius ("r") at specific doses but did not affect neurite number or length.
*, $p < 0.05$, significantly different as compared to control group.



DOI and **Psilocybin** dose-dependently reduced marble burying behavior in mice, suggesting an attenuation of compulsivity and repetitive behaviors. Both compounds attenuated scopolamine-induced spontaneous alternation deficit, thus mitigating cognitive impairments.

Key points

- **DOI** and **Psilocybin** induce distinct morphological neuroplastic effects on neuronal cultures, highlighting their capacity to enhance synaptic plasticity through different mechanisms.
- **DOI** and **Psilocybin** reduced frenetic marble burying behavior in a dose-dependent manner, indicating potential to alleviate repetitive and stereotypic behaviors.
- **DOI** and **Psilocybin** improved reduced spontaneous alternation behavior in scopolamine-treated mice, suggesting they mitigate cognitive deficits such as impaired working memory and attention.

Conclusion:

- Both **DOI** and **Psilocybin** demonstrate potential as therapeutic agents for addressing behavioral and cognitive dysfunctions associated with **Alzheimer's disease** (AD).
- Their unique neuroplastic profiles provide insights into tailoring psychedelics for specific behavioral and neurological outcomes in neurodegenerative disorders.