Converging behavioral effects of diverse psychedelics via shared serotonergic pathways: 5-MeO-DMT exhibits neuroplastic and therapeutic potential

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NEUROFIT PRECLINICAL RESEARCH

Background / Objective

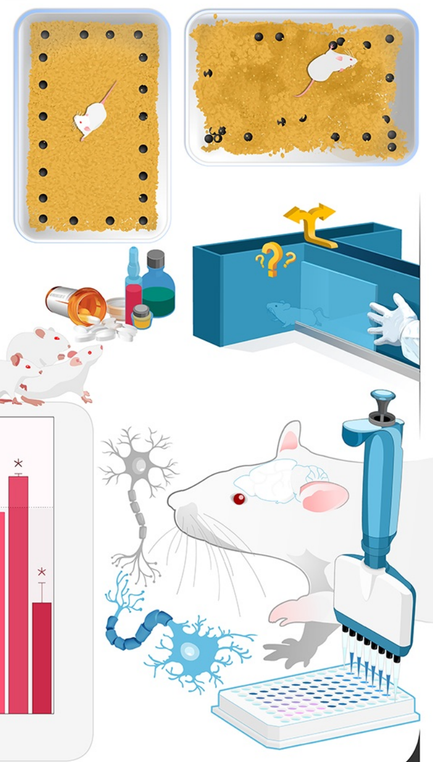
- Psychedelics targeting **serotonergic receptors** show promise as psychoplastogens to counter cognitive and behavioral deficits in Alzheimer's disease (AD). **5-MeO-DMT**, with high affinity for **5-HT$_1$A** over **5-HT$_2$A** receptors, may produce fewer visual hallucinations than classic psychedelics, while its additional activity at melatonin receptors could offer unique therapeutic advantages.
- The objective of the present work was to compare the **neuroplastic** and **behavioral effects** of **5-MeO-DMT** with **DOI** and **Psilocybin**, and explore its potential as a fast-acting, low-burden therapeutic.

Material and Methods

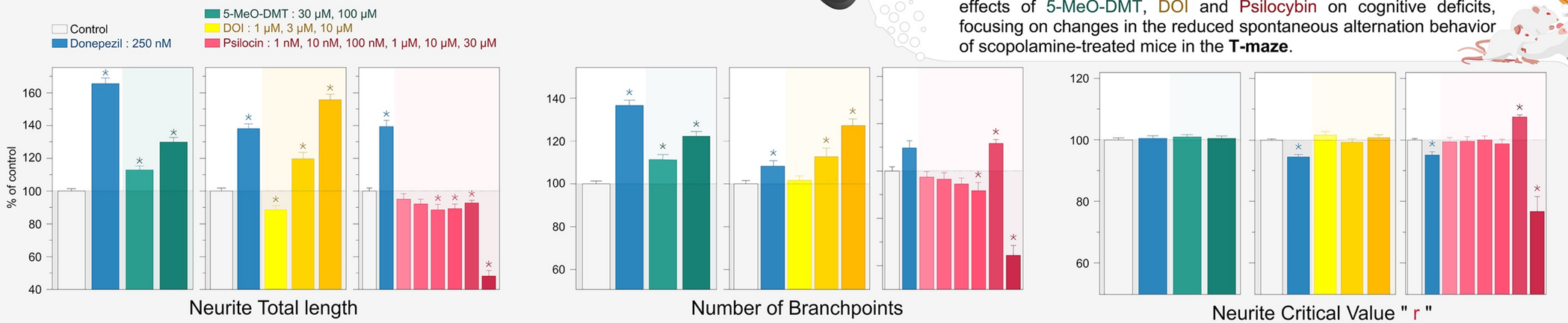
- **Primary neuronal cultures from the cortex of rat embryos:**

  Assessment of 5-MeO-DMT, 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 ")

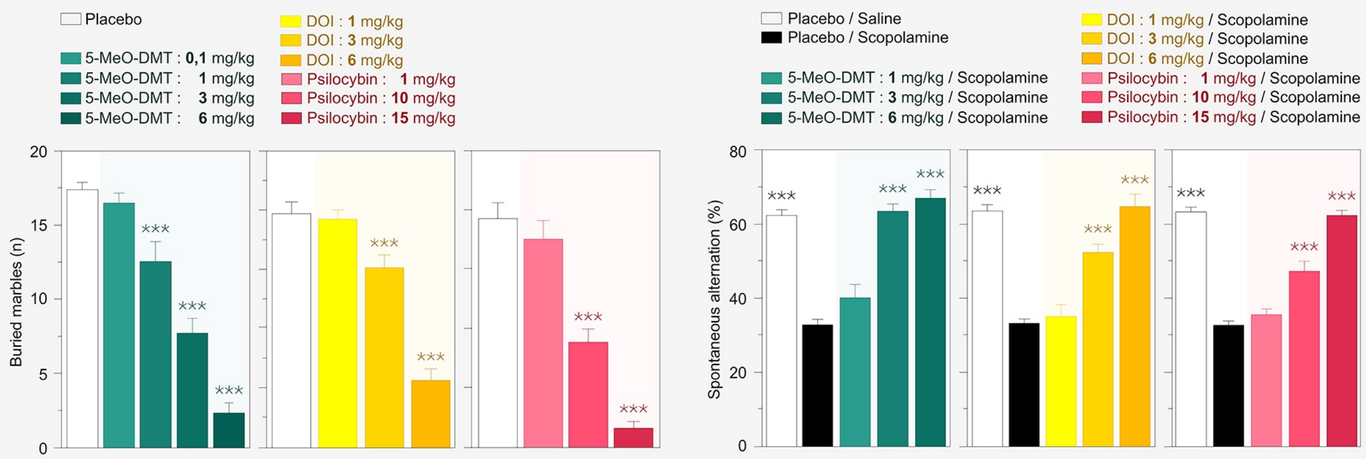
- **Mouse behavioral models:**
  - **Marble Burying Task**: Assessed the effects of 5-MeO-DMT, DOI and Psilocybin on repetitive and stereotypic behaviors, measured by the change in frenetic **Marble Burying behavior**.
  - **Scopolamine-Induced Cognitive Deficit model**: Evaluated the effects of 5-MeO-DMT, DOI and Psilocybin on cognitive deficits, focusing on changes in the reduced spontaneous alternation behavior of scopolamine-treated mice in the **T-maze**.



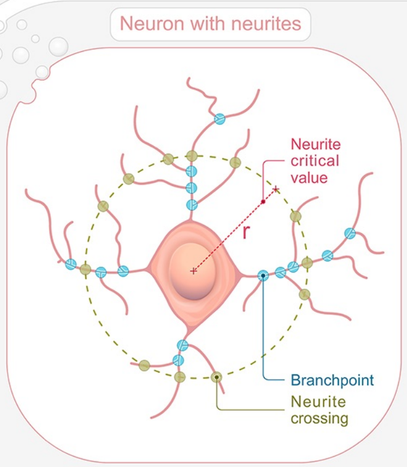
Results



5-MeO-DMT and DOI dose-dependently increased neurite total length, and branch points but not neurite critical value " r ". Psilocybin (Psilocin) increased branch points and the neurite critical radius (" r ") at specific doses but did not affect neurite length. *, $p < 0.05$, significantly different as compared to control group (higher significance also marked as *)



5-MeO-DMT, 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. ***, $p < 0.001$ vs. Placebo or Placebo / Scopolamine, as appropriate.



Key points

5-MeO-DMT promotes neurite outgrowth and branching in cortical neurons, showing neuroplastic effects comparable to DOI but distinct from those induced by Psilocybin.

Despite a differential neuroplastic profile compared to Psilocybin, all three compounds—5-MeO-DMT, DOI, and Psilocybin—reduce frenetic marble-burying behavior and reverse scopolamine-induced cognitive deficits in mice, demonstrating comparable behavioral efficacy in models of cognitive rigidity and impairment.

Conclusion

5-MeO-DMT, DOI, and Psilocybin all show promise as therapeutic agents for cognitive and behavioral dysfunctions linked to Alzheimer's disease. The relatively higher affinity of 5-MeO-DMT for **5-HT$_1$A** receptors likely contributes to its reduced visual hallucinogenic profile compared to other psychedelics, while still promoting neuroplasticity and behavioral improvements via overlapping serotonergic mechanisms.

Its distinct receptor profile, including melatonergic activity and rapid action, may offer clinical advantages and warrants further investigation.