



BEHAVIORAL EFFECTS OF A 14-DAY REPEATED TREATMENT WITH PSILOCYBIN AT A LOW NON-PSYCHEDELIC DOSE: A PRELIMINARY STUDY IN C57BL/6J MICE

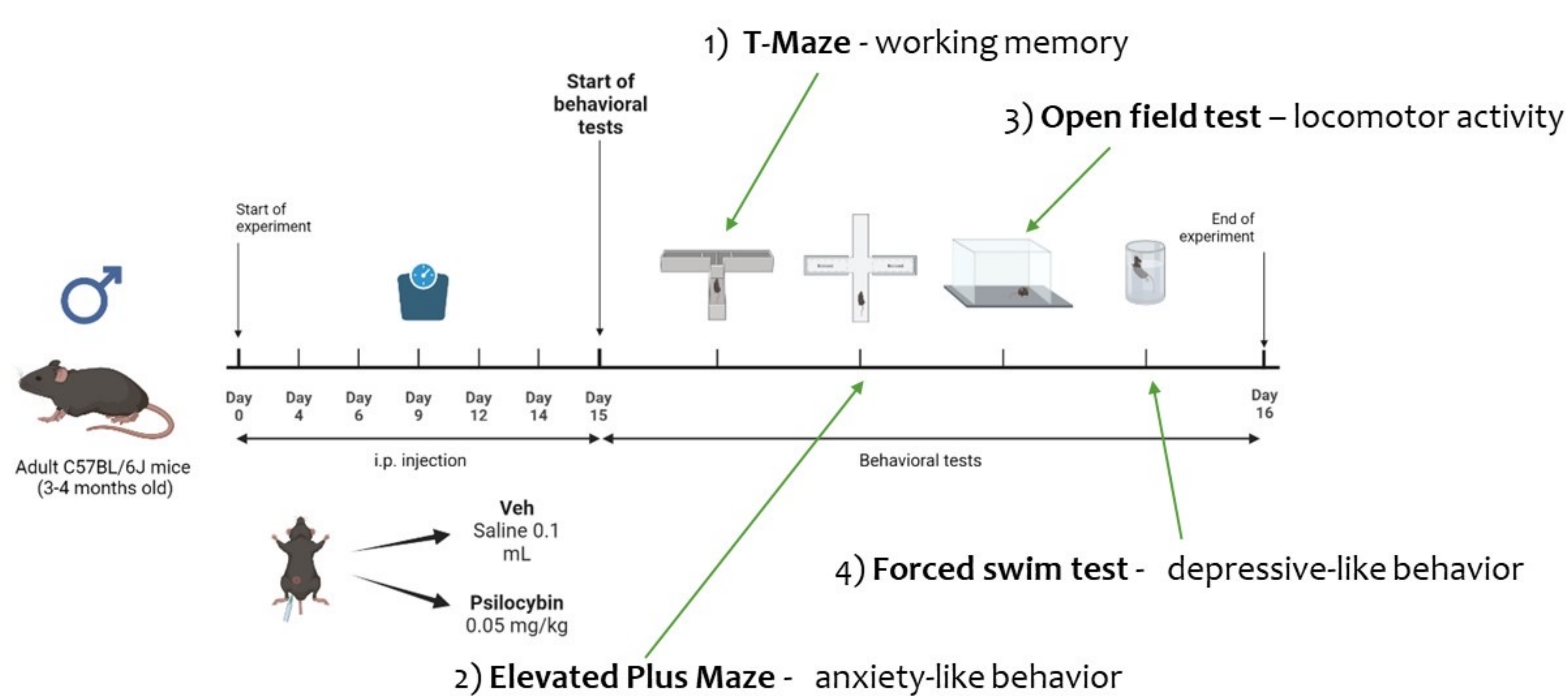
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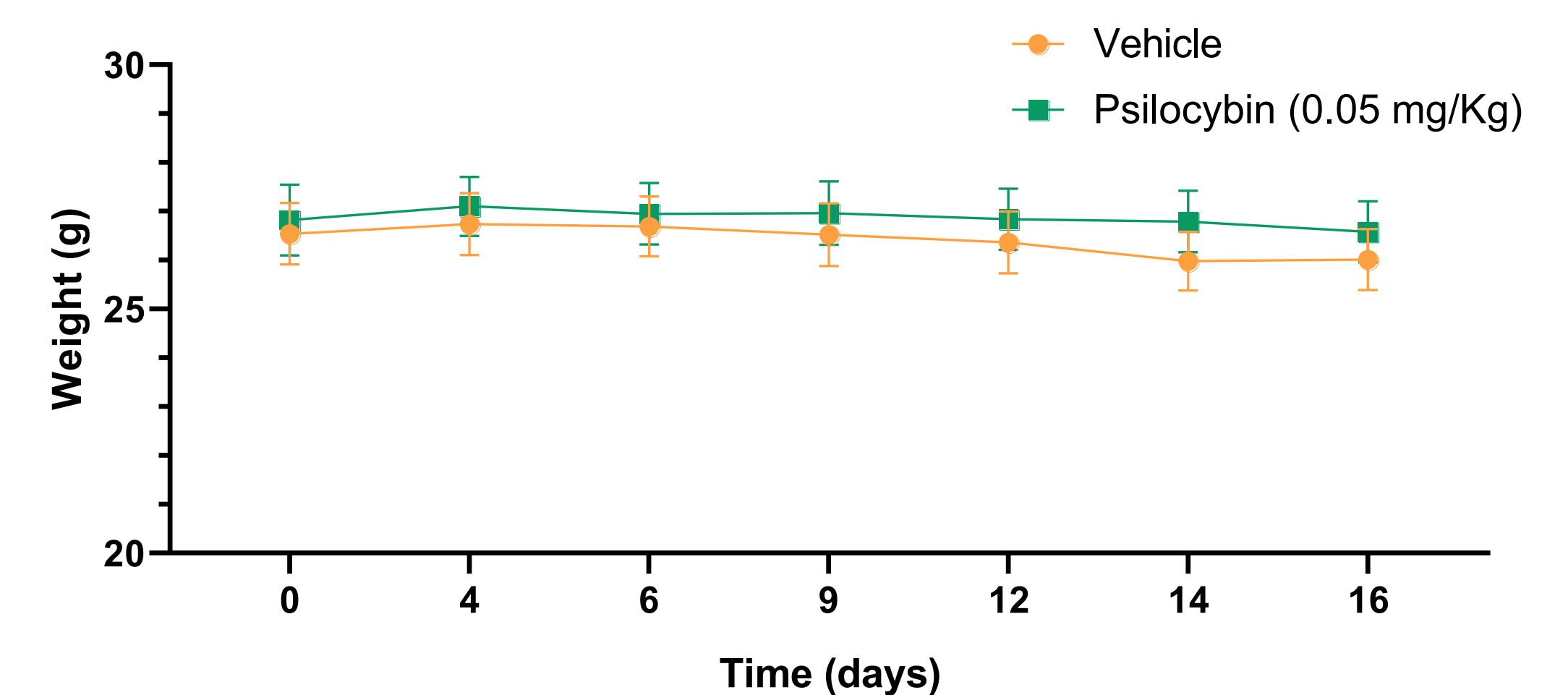
INTRODUCTION

Psilocybin is a natural alkaloid derived from tryptamine with psychedelic activity, produced by more than 200 species of mushrooms of the genus *Psilocybe*. Psilocybin is an inactive compound (prodrug), but once ingested, it is rapidly dephosphorylated into the active compound psilocin, which is responsible for its activity. In humans, its effects at psychedelic dosages include prominent visual hallucinations, changes in perception, a distorted sense of time, and the perception of spiritual experiences. Adverse reactions such as nausea/vomiting, headache, increased blood pressure and panic attacks have been described, but they appear to be dose dependent and tend to occur exclusively at high psychedelic doses that lead to a relatively high occupancy of the serotonin 5-HT_{2A} receptor (around 70%), for which psilocin has high affinity and agonist effect (Insera et al., 2021). However, it has been observed that at non-psychedelic doses, improved perception of colors, contrasts and stereopsis may be present, and in any case these effects may precede and persist after the psychedelic experience (Kometer 2018). Encouraging results are showing that 1 or 2 administrations of psilocybin at a psychedelic dose together with psychological support produces antidepressant effects and can improve post-traumatic stress symptoms, reduce anxiety levels, and can help for smoking cessation (Kisely et al., 2023). More recently, several clinical studies have demonstrated that when psilocybin is used in non-psychedelic, non-intoxicating doses, the so-called microdoses, it has a safety profile very similar to placebo (Studerus et al. 2011, Carhart-Harris et al. 2016; Carhart-Harris et al. 2021). The practice of microdosing is thought to improve mood, cognitive function and mental health in general. However, preclinical and clinical studies on the effects of microdosing psilocybin are still missing. For this reason, in this preliminary study we aimed at evaluating in mice the effects of a 14-day treatment with a microdose of psilocybin (0.05 mg/Kg, intraperitoneal injection) on different behavioral paradigms of anxiety-, depression- and cognitive-like behaviors.

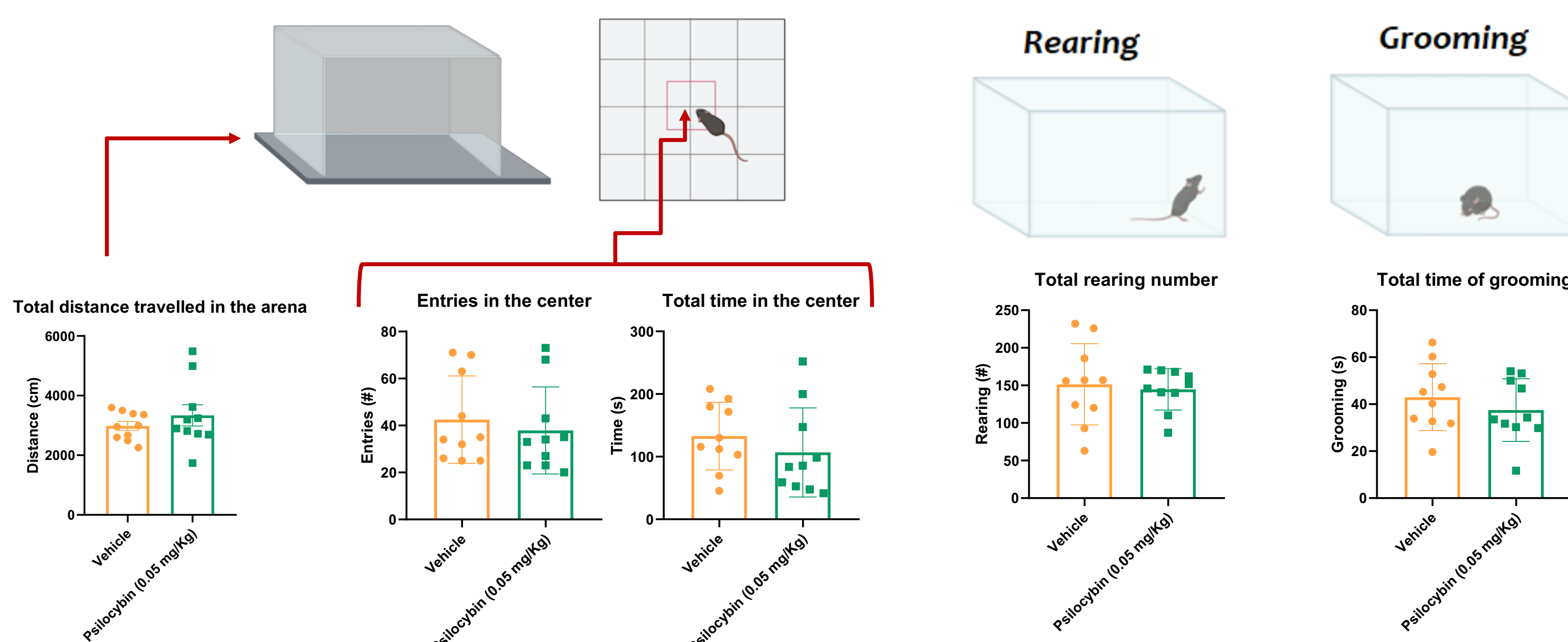
Experimental timeline



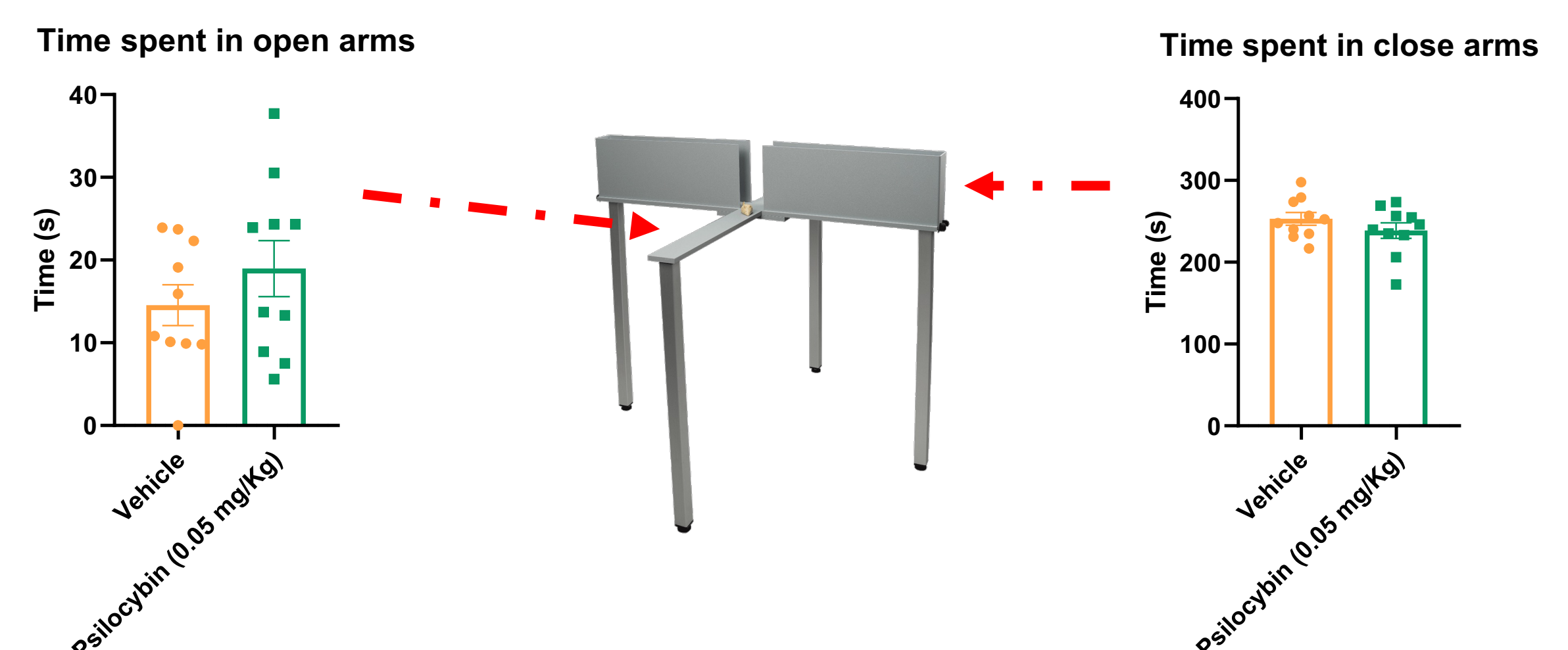
We did not observe any effect of the treatment with psilocybin compared to that of vehicle on the weight of the mice over the two weeks



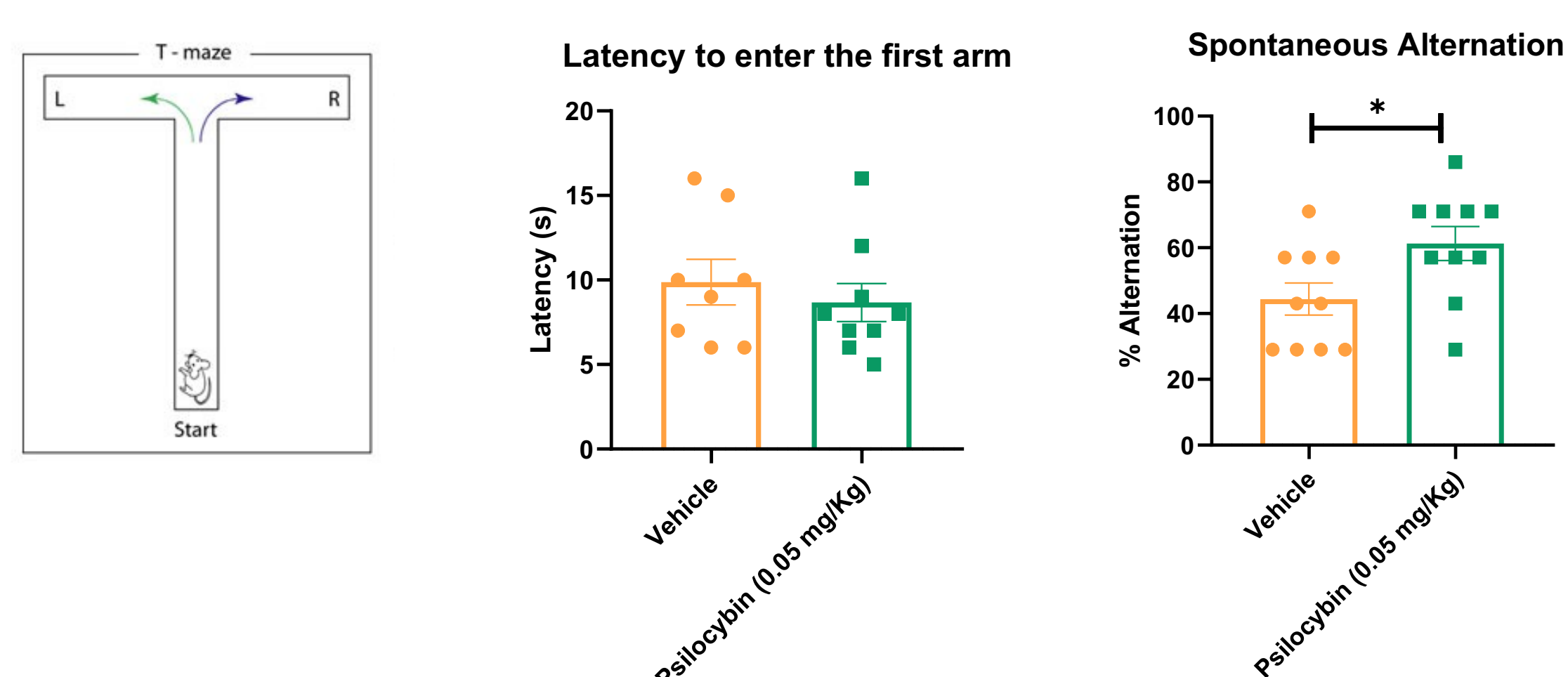
No effects of the 14 days treatment with psilocybin was observed in the Open Field Test



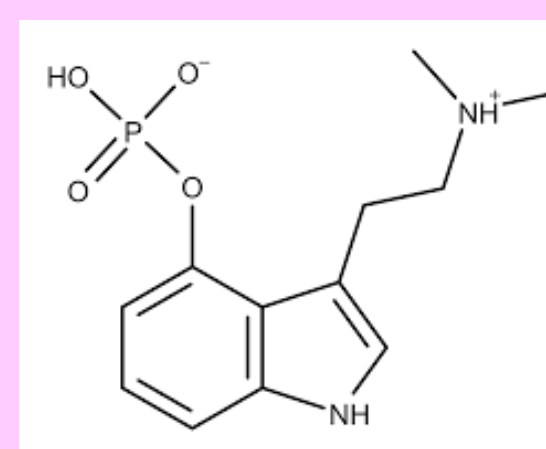
No effects of the 14 days treatment with psilocybin was observed in the Elevated Plus Maze Test



14 days treatment with psilocybin improved spatial working memory in the T-maze Test

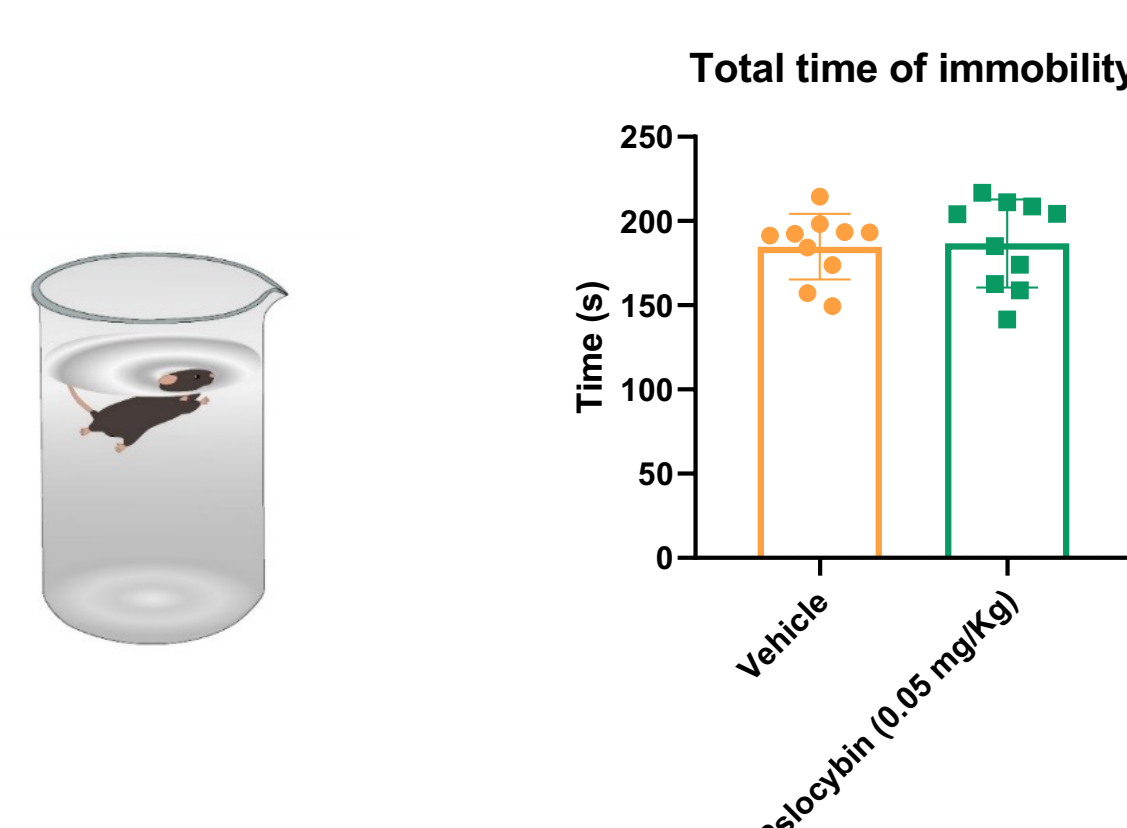


Daily intraperitoneal injection for 14 days of a microdose (0.05 mg/Kg)



- No changes in weight
- No effects in the Open Field Test
- No effects in the Elevated Plus Maze Test
- No effects in the Forced Swim Test
- Increase in the percentage of correct spontaneous alternations in the T-Maze Test

No effects of the 14 days treatment with psilocybin was observed in the Forced Swim Test



14 days treatment with a microdose of psilocybin is apparently safe and, compared with vehicle, does not seem to affect multiple tests of emotional behavior. Interestingly, we have observed that psilocybin induces a statistically significant enhancement of the functioning of the spatial working memory.

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Franco Folli, Marco Pappagallo, Paolo L. Manfredi are paid consultants for Relmada Therapeutics.

Sara De Martin, Andrea Mattarei, Franco Folli, Marco Pappagallo, and Paolo L. Manfredi are applicants on patents related to psilocybin and its derivatives.

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