Rapid acting antidepressants in motivation: the effect of psychedelic drugs in the rat progressive ratio task.

Transpharmation
Science that translates into results

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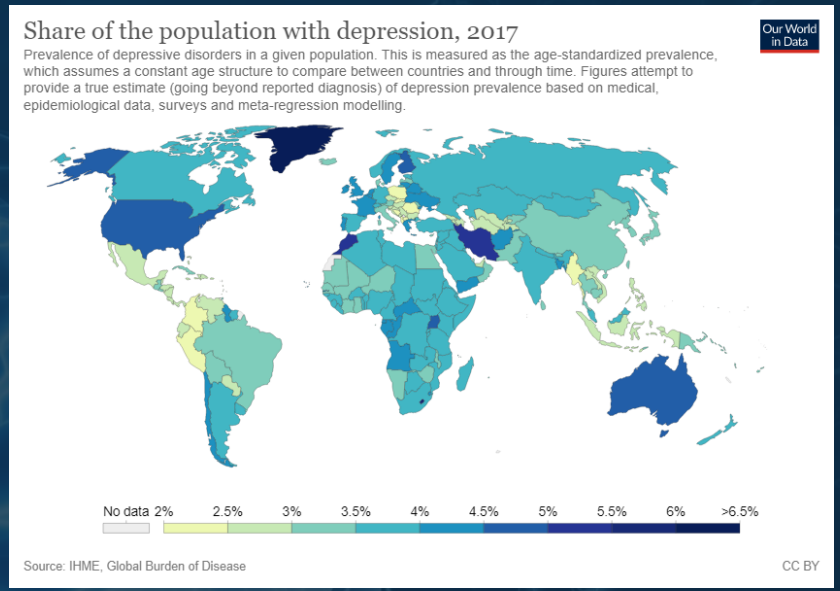
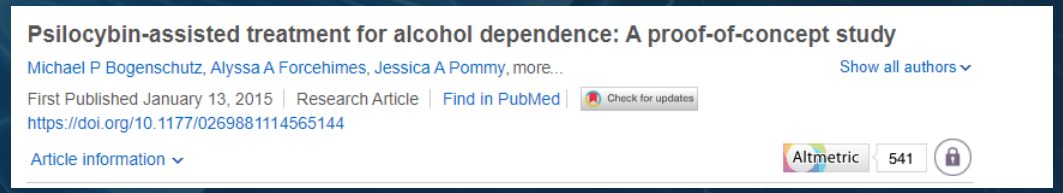
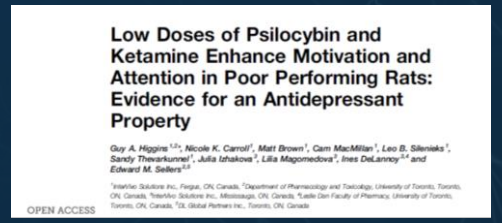
Background

- The global burden of major depressive disorder is increasing
- The shift away from ‘gold standard’ antidepressant treatments towards novel antidepressant therapies as a solution has been growing
- More recently there has been a focus on psychedelic compounds acting through the serotonin 2A receptor that have demonstrated clinical efficacy in major depressive disorder and treatment resistant depression. Dysregulated motivation and reward processing have been linked to putative endophenotypes in several neuropsychiatric conditions and represent a potential transdiagnostic treatment target.
- Recently a study was published on the efficacy of low-dose ketamine and psilocybin at improving motivation in low performing rats on a progressive ratio task
- The current study aims to compare low doses of ketamine as well as a low and a psychoactive dose of the psychedelic drugs 2,5-dimethoxy-4-iodoamphetamine (DOI) and psilocybin in the progressive ratio task in rats.







The Progressive Ratio Task

Operant based task designed to measure motivation

Animals are placed on food restriction (~85% bodyweight) and trained to respond to a lever presentation by pressing it to receive a reward. In this case a 45mg sucrose pellet

Training on the task was at a fixed ratio of 1 (1 press = reward)

In the progressive ratio section of the task the number of responses required to obtain a food pellet is increased for successive reinforcers.

Responses for successive reinforcers increased according to the progression dictated by a sequence, derived from the equation: ratio = **[5 × e(0.2 × reinforcer #)**

The two main measures in the task: Number of lever presses and the break point (trial that the animal reaches).

A rat was assumed to have reached the break point if it failed to receive a reward for 20 min.

The Progressive Ratio Task: Study Design

Study 1: Male SD rats split into groups of 9-10.
Treatments were vehicle and ketamine at 0.1, 0.5mg/kg, s.c.
Behaviour was scored at 30 minutes, then daily for 3 days and at days 9, 10

Study 2: One group of male SD rats (n=25) were treated with DOI 1mg/kg s.c., behaviour was scored at 30 minutes, then daily for 5 days.

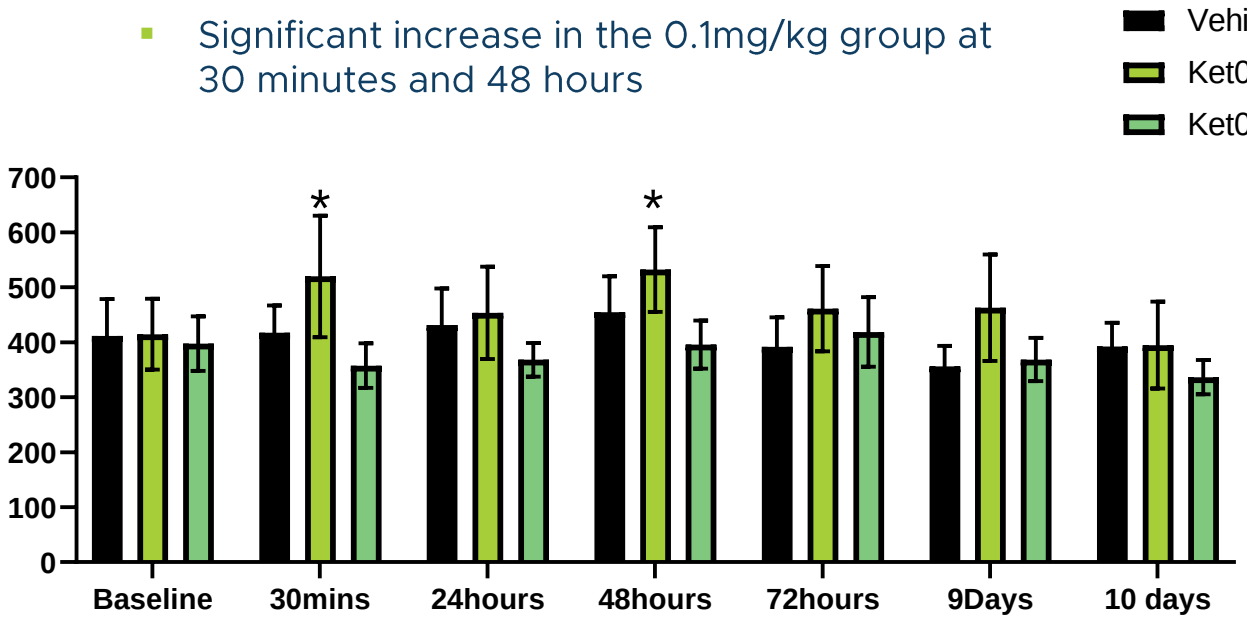
Study 3: Male SD rats split into groups of 9-10.
Treatments were vehicle and DOI at 0.2 & 1mg/kg.
All treatments were given s.c. and behaviour was scored at 30 minutes, then daily for 7 days

Study 4: Male SD rats split into groups of 9-10.
Treatments were vehicle and psilocybin at 1 & 3mg/kg.
All treatments were given s.c. and behaviour was scored at 30 minutes, then daily for 21 days and at 28 days post administration.

Acute effects of low dose ketamine

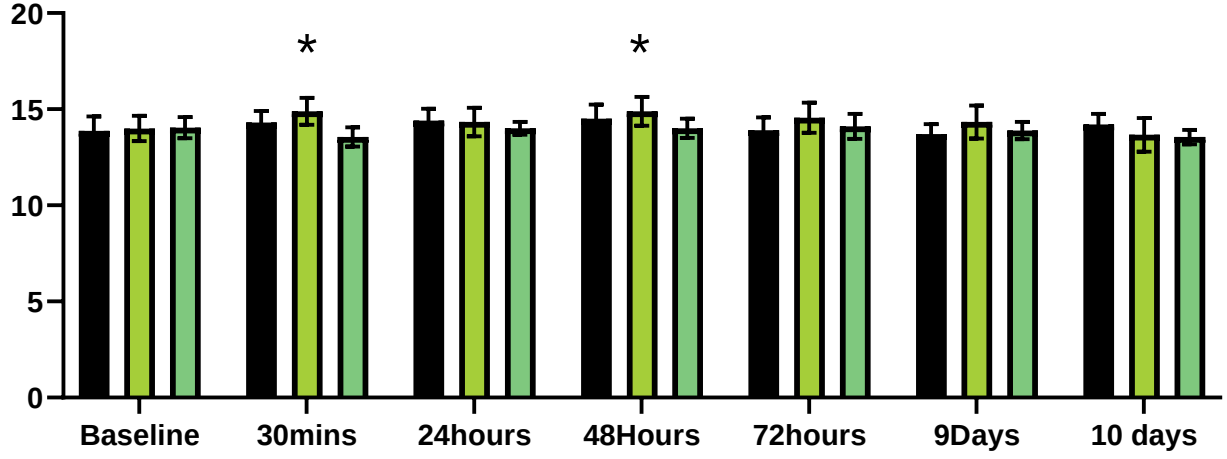
Lever Presses

- Significant increase in the 0.1mg/kg group at 30 minutes and 48 hours



Break Point

- Significant increase in the 0.1mg/kg group at 30 minutes and 48 hours

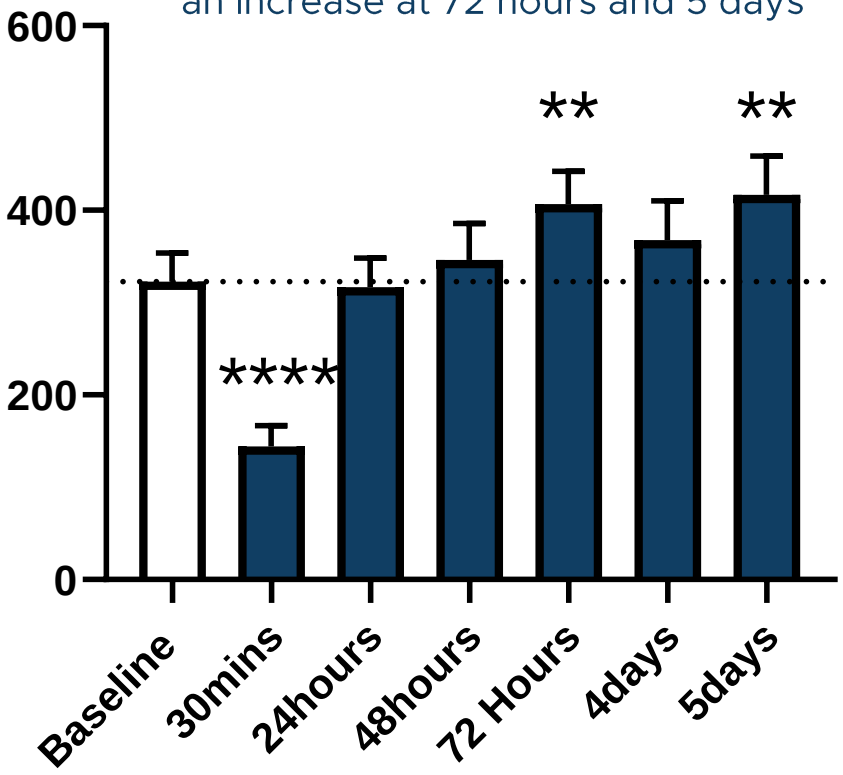


* Significant compared to Baseline group. Mean ± S.E.M. Two-way repeated measures ANOVA with Fishers LSD post-hoc

Effects of acute treatment with DOI (1mg/kg, n=25)

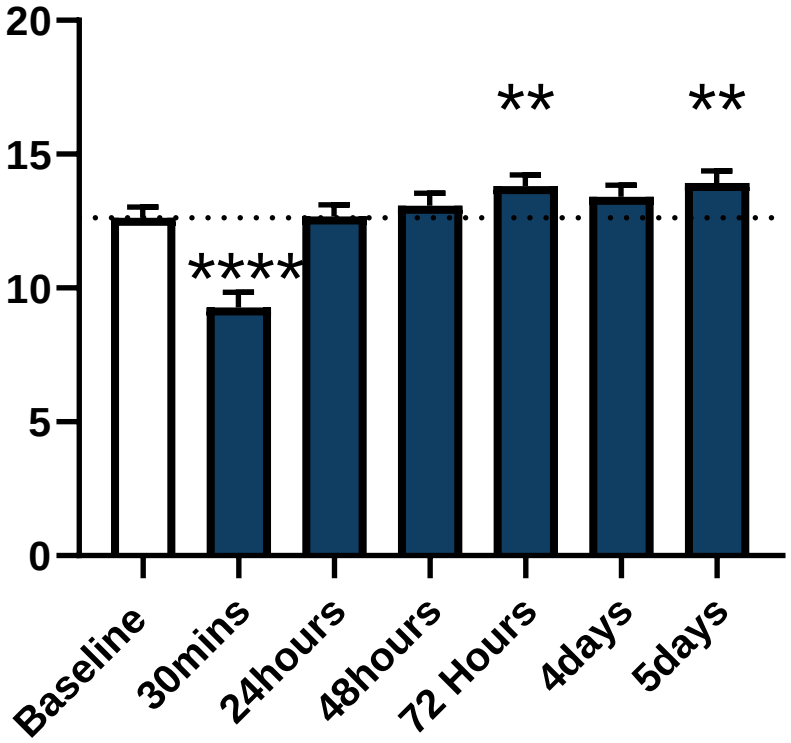
Lever Presses

- Decrease at 30 minutes followed by an increase at 72 hours and 5 days



Break Point

- Decrease at 30 minutes followed by an increase at 72 hours and 5 days



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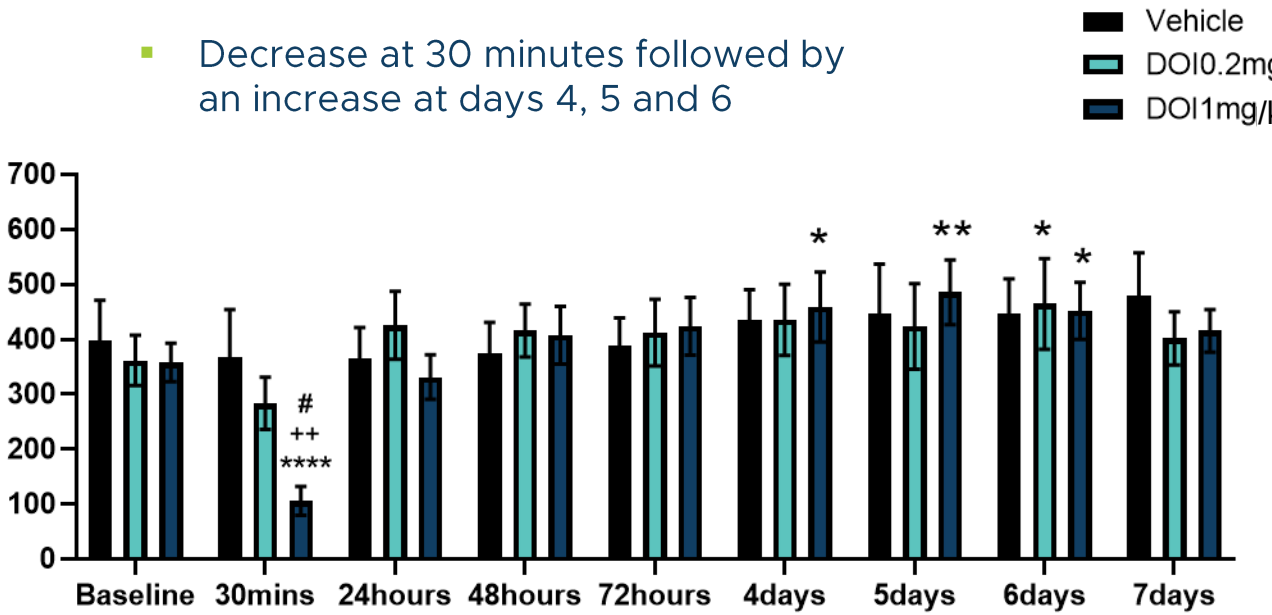
Effects of acute treatment with DOI (0.2 and 1mg/kg, n=9-10)

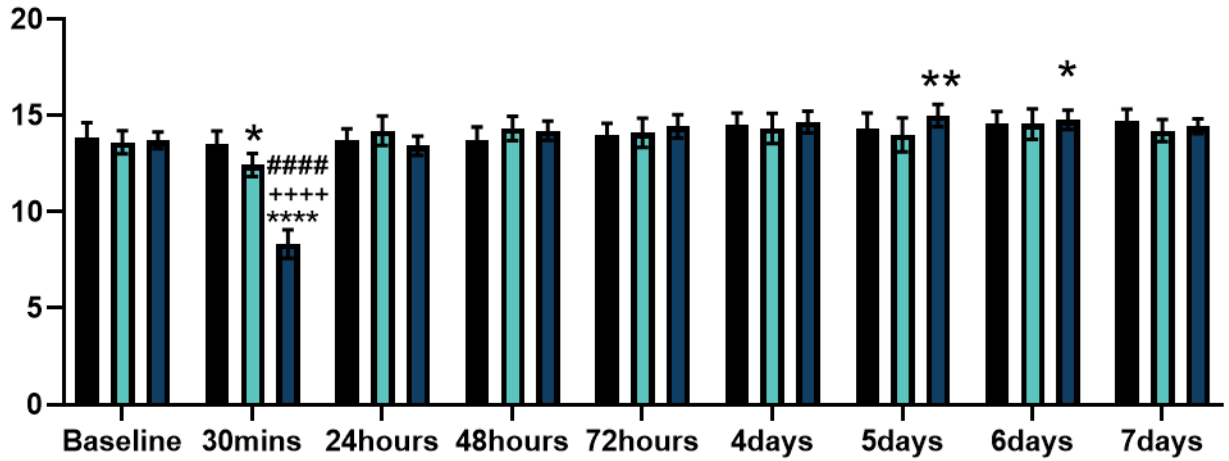
Lever Presses

- Decrease at 30 minutes followed by an increase at days 4, 5 and 6



Break Point

- Dose dependent decrease at 30 minutes followed by a significant increase in the 1mg/kg group at days 5 and 6



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+ Significant compared to Vehicle group. Mean ± S.E.M. Two-way repeated measures ANOVA with Fishers LSD post-hoc

Significant compared to 0.2mg/kg group. Mean ± S.E.M. Two-way repeated measures ANOVA with Fishers LSD post-hoc

Effects of acute treatment with psilocybin (1 and 3mg/kg, n=9-10)

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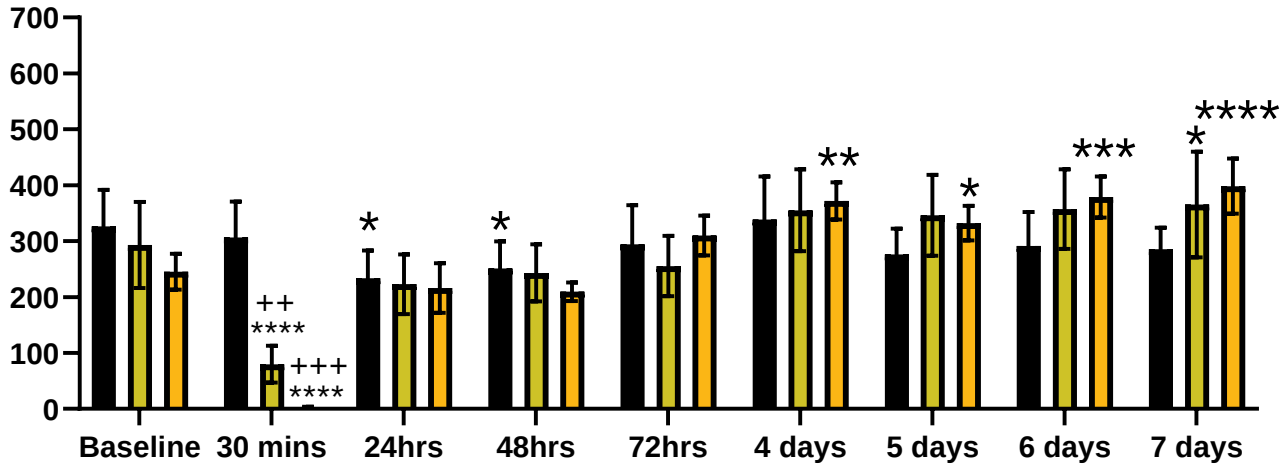
Lever Presses

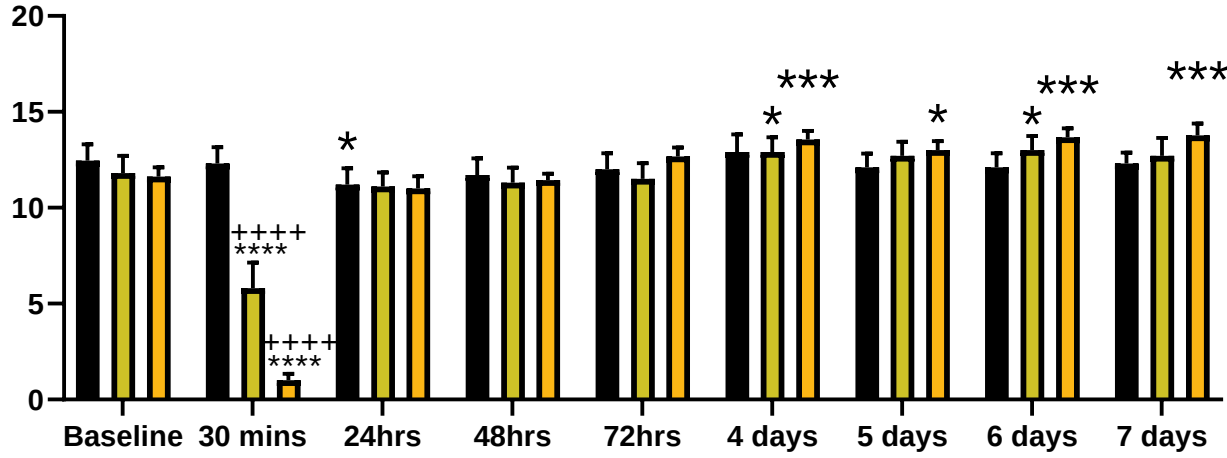
- Dose dependent decrease at 30 minutes followed by a significant increase in the 1mg/kg group at day 7 and at days 4, 5, 6 and 7 for the 3mg/kg group



Break Point

Veh
1mg/kg
3mg/kg

- Dose dependent decrease at 30 minutes followed by a significant increase in the 1mg/kg group at day 6 and at days 4, 5, 6 and 7 for the 3mg/kg group



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+ Significant compared to Vehicle group. Mean ± S.E.M. Two-way repeated measures ANOVA with Fishers LSD post-hoc

Long-term effects of acute treatment with psilocybin (1 and 3mg/kg, n=9-10)

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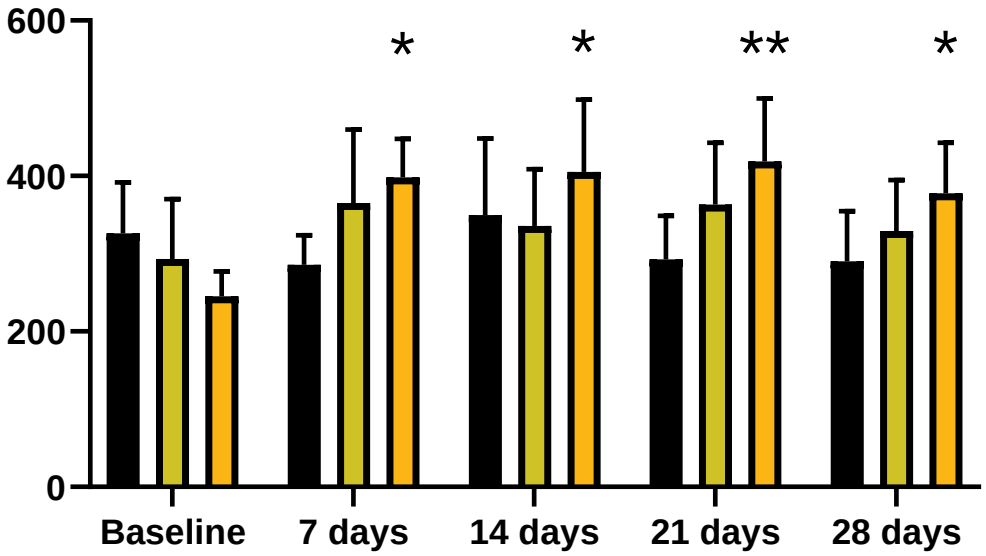
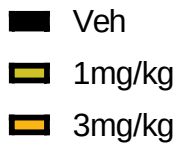
Lever Presses

- Significant increases at all four timepoints assessed in the 3mg/kg group





Break Point

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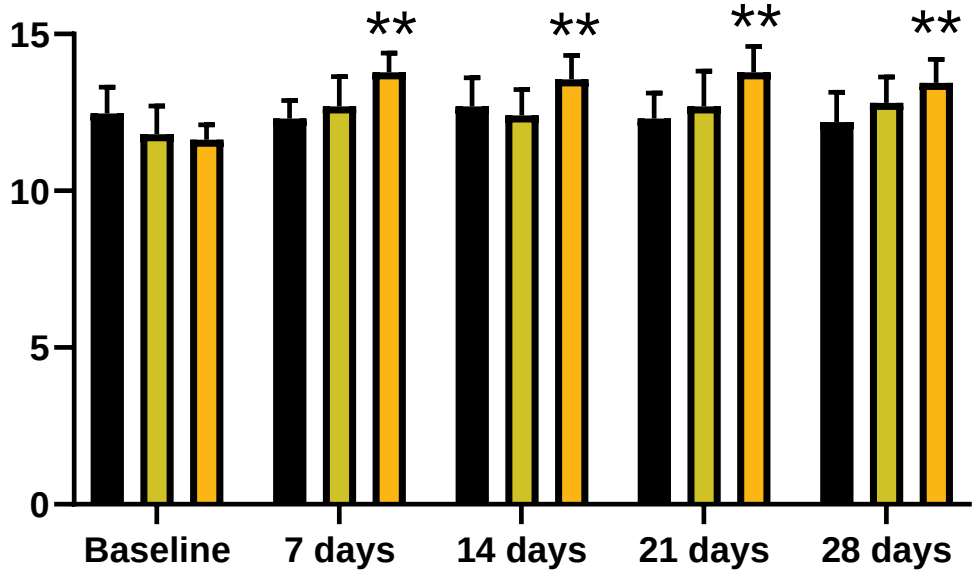

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Summary/Conclusions:

- Study 1: Significant increases with 0.1mg/kg of ketamine at 30 mins and 48 hours
- Study 2: DOI (1mg/kg) demonstrates an acute reduction in performance at 30 minutes followed by a recovery at 24 hours and a gradual improvement with significant increases at days 3 and 5.
- Study 3: Both doses of DOI acutely impairs performance, this returns to baseline at 24 hours and increases significantly across the week with a peak around day 5 compared to baseline and returning to normal at day 7. Studies 2 + 3 show a similar response to DOI at 1mg/kg s.c.
- Study 4: A significant and dose dependant reduction in performance after acute administration with psilocybin was observed. This was followed by a recovery at 24 hours and a gradual improvement leading to significant improvement by day 4 and continuing until 7 days in the 3mg/kg group. This significant improvement in the 3mg/kg group compared to baseline continued for 4 weeks post a single injection
- The current studies suggest psychedelic compounds (DOI and psilocybin) at psychoactive doses cause an initial disruption in performance followed by a gradual and potentially long-term sustained improvement in motivated behaviour assessed in this task.
- Future studies will look to replicate the findings observed and assess other psychedelic compounds in the task as well as assessing the psychedelic compounds tested in the current study in an animal model of depression.

