

# Preclinical Studies on the Anti-Obsessional Properties of Psilocybin



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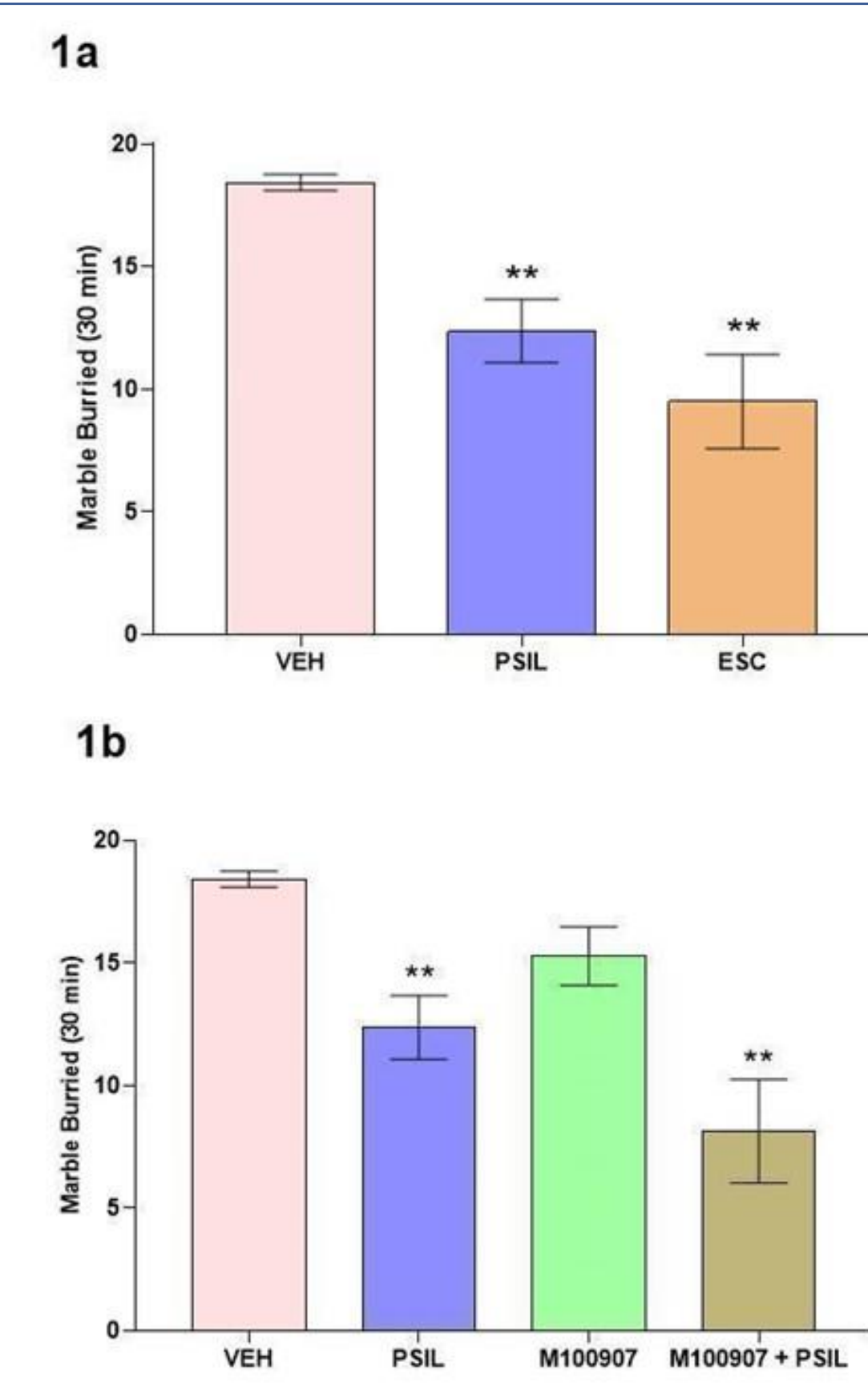


## BACKGROUND

- There is increasing interest in the potential role of psychedelic compounds in the treatment of psychiatric disorders.
- Notwithstanding the relative efficacy of serotonin uptake blockers and cognitive-behavioral therapy (CBT) in obsessive compulsive disorder (OCD), a third or more patients with OCD do not respond to standard treatments.
- Reports from one clinical trial and several preclinical studies suggest that 5-HT<sub>2A</sub> receptor agonists with psychedelic properties may have unique efficacy in the treatment of OCD.
- The aims of this study were to:
  - Further evaluate the role of 5-HT<sub>2A</sub> receptors in the effect of psilocybin on marble-burying, a preclinical screening test in mice for potential anti-obsessional effects.
  - Explore the role of 5-HT<sub>1A</sub> receptors in the anti-marble burying effect of psilocybin
  - Examine potential use the 5-HT<sub>1A</sub> receptor partial agonist, buspirone, as a treatment for OCD concurrent with psilocybin.

## METHODS

- Male ICR mice (30±2 gm) were group housed under a regular 12 hr. light-dark cycle. Drugs were administered by intraperitoneal (i.p.) injection 30 minutes before assessment of marble burying.
- Psilocybin (PSIL) was administered at a dose of 4.4 mg/kg i.p., alone, or preceded by the 5-HT<sub>1A</sub> agonist, 8-OH-DPAT 2 mg/kg; the 5-HT<sub>2A</sub> antagonist, M100907 (volanserin) 2 mg/kg; the 5-HT<sub>1A</sub> partial agonist, buspirone, 5 mg/kg; or the 5-HT<sub>1A</sub> antagonist, WAY100635 2 mg/kg; or combinations.
- Escitalopram (ESC, 5mg/kg i.p.) was administered as a positive control.
- Marble burying was measured in a cage in which 20 marbles were placed on top of the sawdust. Over 30 minutes, the number of marbles buried by the mouse was counted.
- Head twitch response (HTR) induced by psilocybin alone or in combination with buspirone, was examined in a magnetometer-based assay.



**Figure 1: MARBLE BURYING: PSILOCYBIN, ESCITALOPRAM AND PSILOCYBIN + A 5-HT<sub>2A</sub> ANTAGONIST**

**1a:** Effect of psilocybin 4.4 mg/kg and ESC 5 mg/kg on total marbles buried over 30 minutes. One way ANOVA:  $F_{2,35} = 13.32$ ,  $p < 0.0001$ .

\*\* $p < 0.01$  vs. VEH,  $n = 8-16$  (Tukey's multiple comparisons test).

**1b:** Effect of psilocybin 4.4 mg/kg, M100907 2 mg/kg and M100907 2 mg/kg + psilocybin 4.4 mg/kg on total marbles buried over 30 minutes. Two-way ANOVA: M100907  $F_{1,40} = 7.74$ ,  $p = 0.008$ , psilocybin  $F_{1,40} = 24.80$ ,  $p < 0.0001$ , Interaction  $F_{1,40} = 0.169$ ,  $p = 0.68$ .

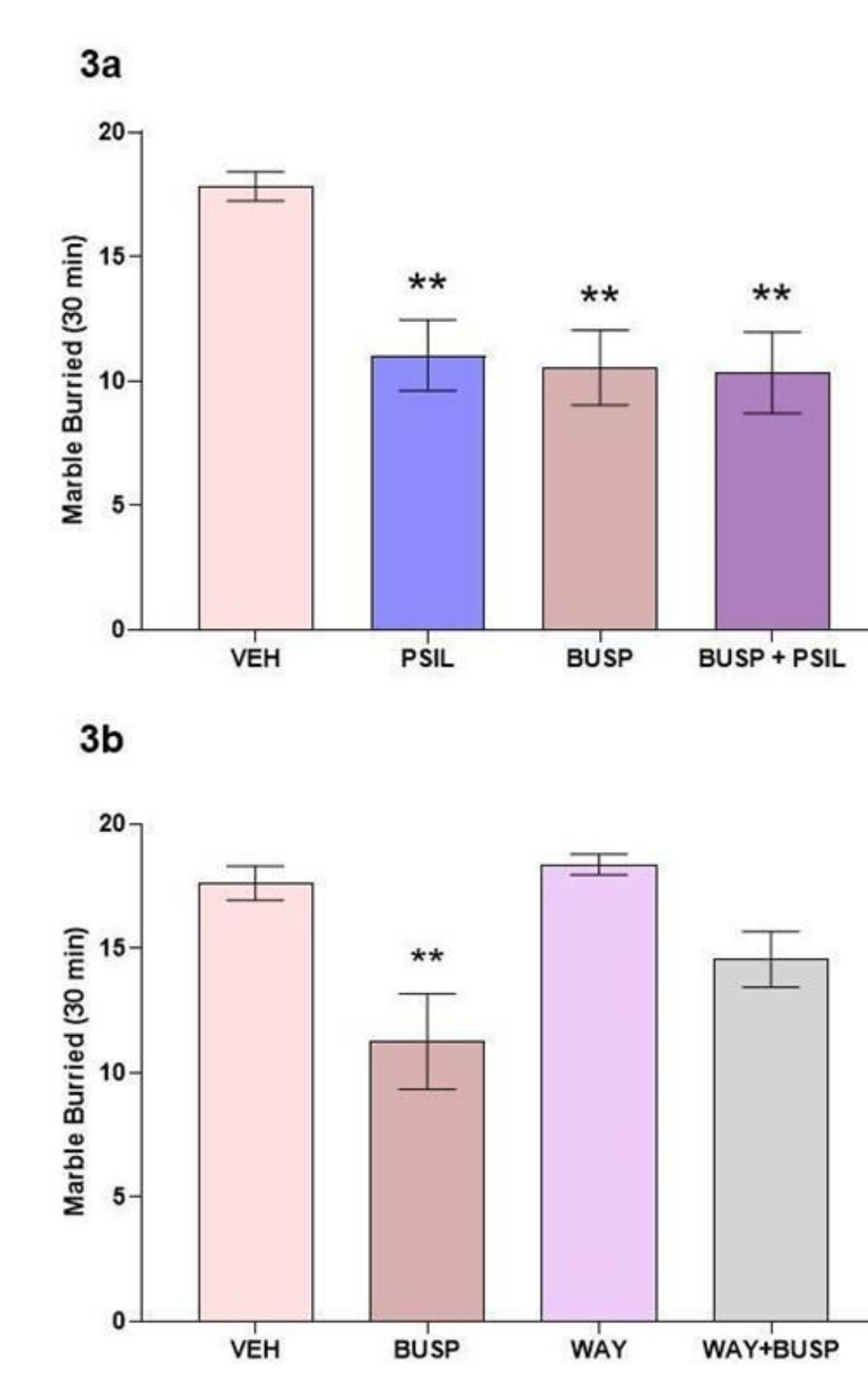
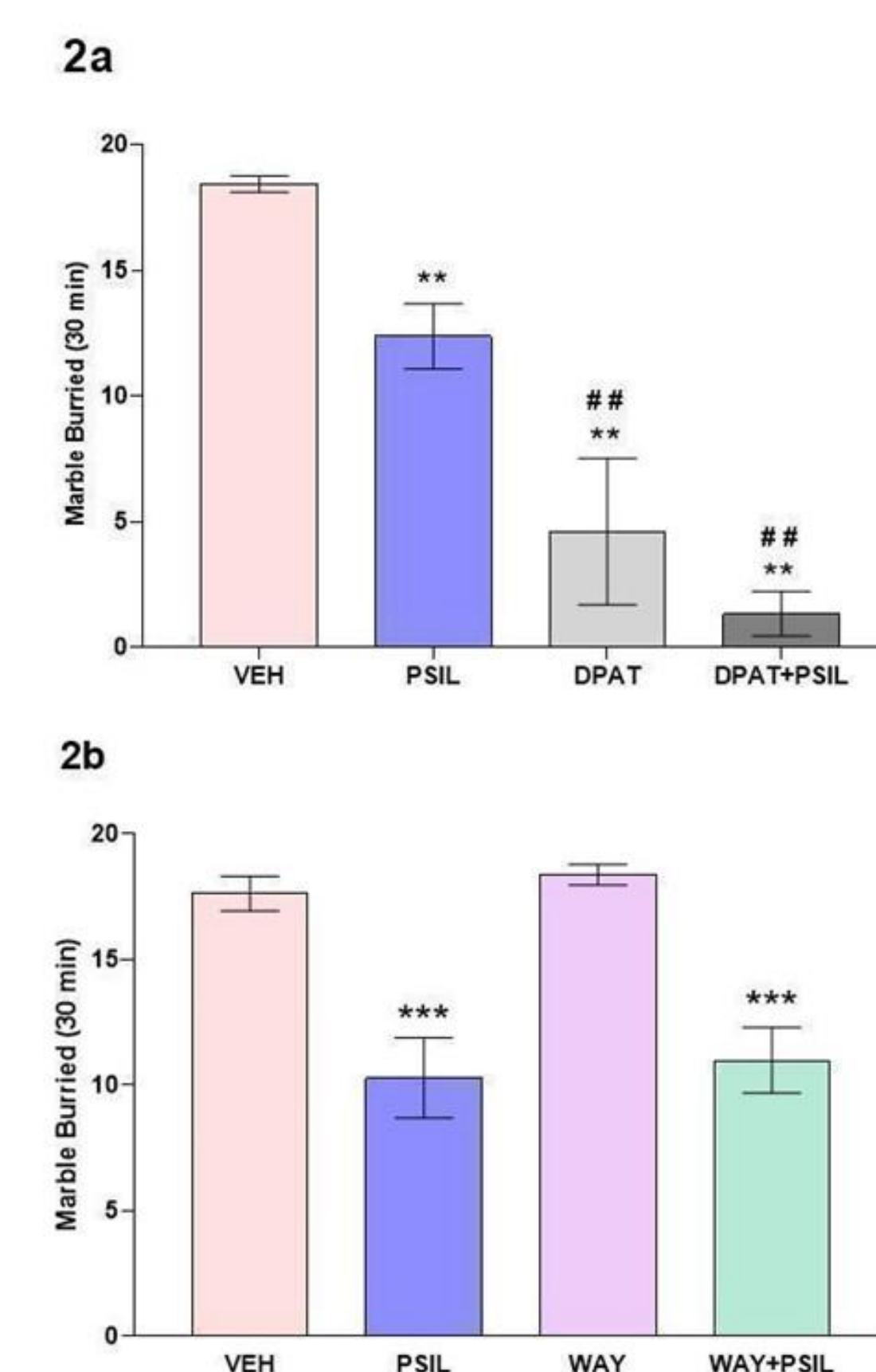
\*\* $p < 0.01$  vs. vehicle,  $n = 7-16$  (Tukey's multiple comparisons test).

**Figure 2: MARBLE BURYING: 5-HT<sub>1A</sub> AGONIST AND 5-HT<sub>1A</sub> ANTAGONIST**

**2a:** Effect of psilocybin 4.4 mg/kg, 8-OH-DPAT 2mg/kg and 8-OH-DPAT 2 mg/kg + psilocybin 4.4 mg/kg on total marbles buried over 30 minutes. Two-way ANOVA: psilocybin  $F_{1,37} = 10.43$ ,  $p = 0.0026$ , 8-OHDPAT  $F_{1,37} = 74.25$ ,  $p < 0.0001$ . Interaction  $F_{1,37} = 0.9324$ ,  $p = 0.3405$

\*\* $p < 0.01$  vs. VEH. ## $p < 0.01$  vs. psilocybin,  $n = 6-16$  (Tukey's multiple comparisons test).

**2b:** Effect of psilocybin 4.4 mg/kg, WAY100635 2 mg/kg and WAY100635 2 mg/kg + psilocybin 4.4 mg/kg on total marbles buried over 30 minutes. Two-way ANOVA: WAY100635  $F_{1,61} = 0.4162$ ,  $p = 0.5212$ , psilocybin  $F_{1,61} = 42.47$ ,  $p < 0.0001$ , Interaction  $F_{1,61} = 0.0003$ ,  $p = 0.9845$ . \*\* $p < 0.001$  vs. vehicle,  $n = 16-17$  (Tukey).



**Figure 3: MARBLE BURYING: BUSPIRONE AND BUSPIRONE+ PSILOCYBIN**

**3a:** Effect of psilocybin 4.4 mg/kg, buspirone 5 mg/kg and buspirone 5 mg/kg + psilocybin 4.4 mg/kg on total marbles buried over 30 minutes. Two-way ANOVA: buspirone  $F_{1,75} = 8.532$ ,  $p = 0.0046$ ; psilocybin  $F_{1,75} = 6.530$ ,  $p = 0.0126$ ; Interaction  $F_{1,75} = 5.805$ ,  $p = 0.0184$

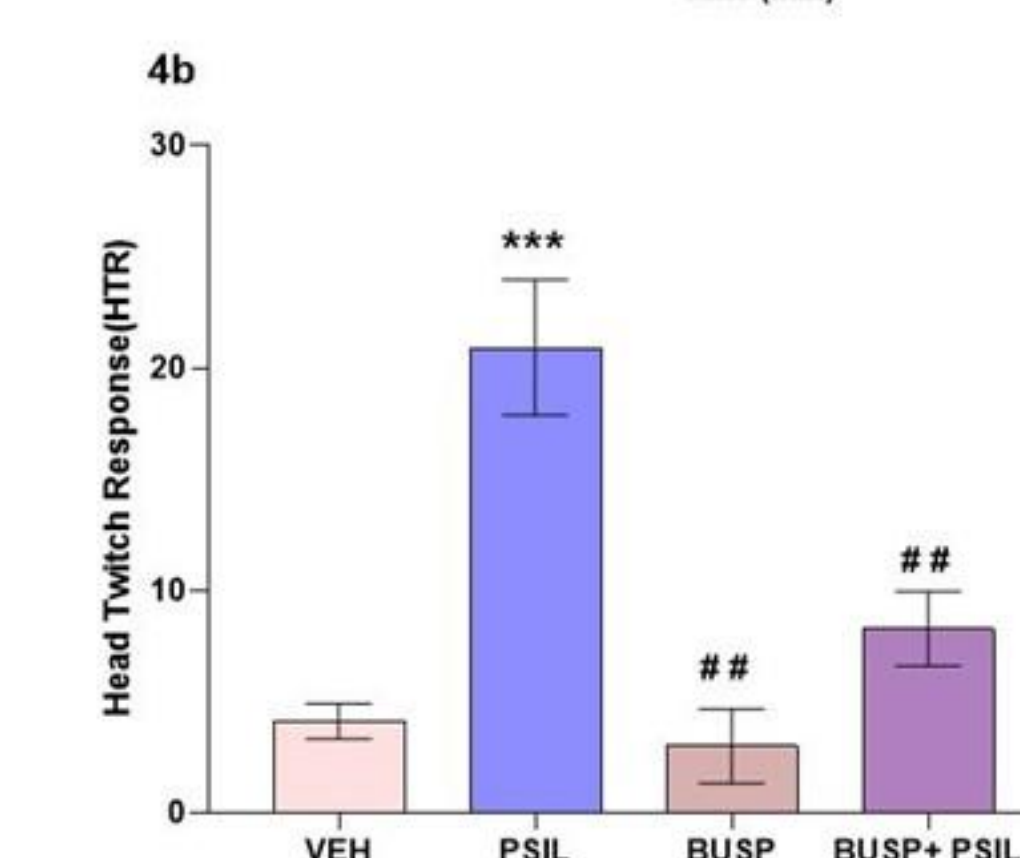
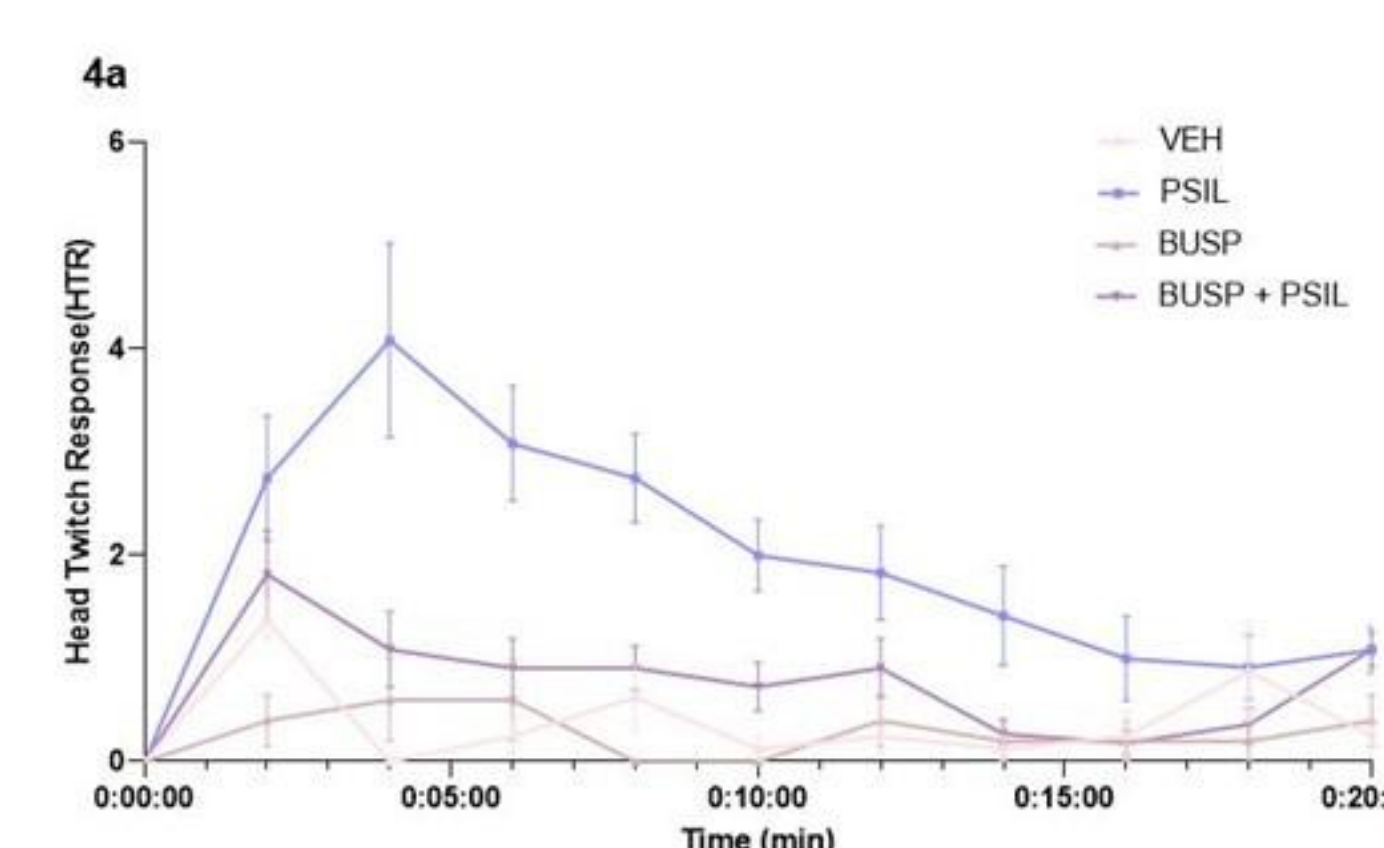
\*\* $p < 0.01$  vs. VEH,  $n = 19-20$  (Tukey's multiple comparisons test).

**3b:** Effect of buspirone 5 mg/kg, WAY100635 2 mg/kg and WAY100635 2 mg/kg + buspirone 5 mg/kg on total marbles buried over 30 minutes. Two-way ANOVA: WAY100635  $F_{1,59} = 3.078$ ,  $p = 0.084$ , buspirone  $F_{1,59} = 19.45$ ,  $p < 0.0001$ , Interaction  $F_{1,59} = 1.219$ ,  $p = 0.274$ . \*\* $p < 0.001$  vs. VEH,  $n = 15-16$  (Tukey).

**Figure 4: HTR: PSILOCYBIN, BUSPIRONE AND BUSPIRONE + PSILOCYBIN**

**4a:** Effect of psilocybin 4.4 mg/kg, buspirone 5 mg/kg and psilocybin 4.4 mg/kg + buspirone 5 mg/kg on HTR over a 20-minute measurement period. Three-way ANOVA: Time  $F_{9,288} = 5.001$ ,  $p = 0.0032$ ; Time x psilocybin  $F_{9,288} = 3.224$ ,  $p = 0.001$ ; Time x psilocybin x buspirone  $F_{9,288} = 2.687$ ,  $p = 0.0072$  (within subject effects). psilocybin  $F_{1,32} = 19.22$ ,  $p = 0.0001$ ; buspirone  $F_{1,32} = 7.483$ ,  $p = 0.0101$ ; psilocybin x buspirone  $F_{1,32} = 5.237$ ,  $p = 0.0289$  (between subject effects).

**4b:** Total HTR over 20 minutes.  $F_{3,32} = 12.87$ ,  $p < 0.0001$ ; \*\*\* $p < 0.001$  vs. vehicle, ## $p = 0.0002$  buspirone vs. psilocybin;  $p = 0.0009$  buspirone + psilocybin vs. psilocybin,  $n = 6-12$  (Tukey)



## RESULTS AND DISCUSSION

- Both psilocybin ( $p < 0.01$ ) and the positive control, escitalopram ( $p < 0.01$ ), significantly reduced marble-burying (Fig. 1a).
- The effect of psilocybin was not attenuated by the 5-HT<sub>2A</sub> antagonist, M100907 (Fig. 1b).
- The 5-HT<sub>1A</sub> agonist, 8-OH-DPAT, reduced marble-burying ( $p < 0.01$ ) (Fig. 2a) as did the 5-HT<sub>1A</sub> partial agonist, buspirone ( $p < 0.01$ ) (Fig. 3a).
- The effect of 8-OH-DPAT was additive to that of psilocybin ( $p < 0.01$ ) (Fig. 1a) but that of buspirone was not (Fig. 2a).
- The 5-HT<sub>1A</sub> antagonist, WAY100635, attenuated the effect of buspirone on marble burying (Fig. 3b) but not the effect of psilocybin (Fig. 2b).
- Psilocybin injections (4.4 mg/kg total) over 3.5 hours had no effect on marble-burying and the effect of bolus injection was not observed 24 hours later (data not shown)
- Co-administration of buspirone with psilocybin attenuated the effect of psilocybin on HTR (Fig. 4a, 4b) (as we have previously observed for 8-OH-DPAT) but not its effect on marble burying.
- Our effects on marble burying were observed at a higher dose of psilocybin than previously reported by Odland et al (2021) in female NMRI mice and by Matsushima et al (2009) in male ICR mice. The role of gender and strain effects on the anti-marble burying effect of psilocybin in mice remains to be further evaluated.

## CONCLUSIONS

- Neither 5-HT<sub>2A</sub> nor 5-HT<sub>1A</sub> receptors are pivotally implicated in the effect of psilocybin on marble-burying.
- Co-administration with buspirone may attenuate the psychedelic effects of psilocybin without impeding its anti-obsessional effects.

## REFERENCES

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