

**Article Title:** MDMA and memory, addiction, and depression: dose-effect analysis

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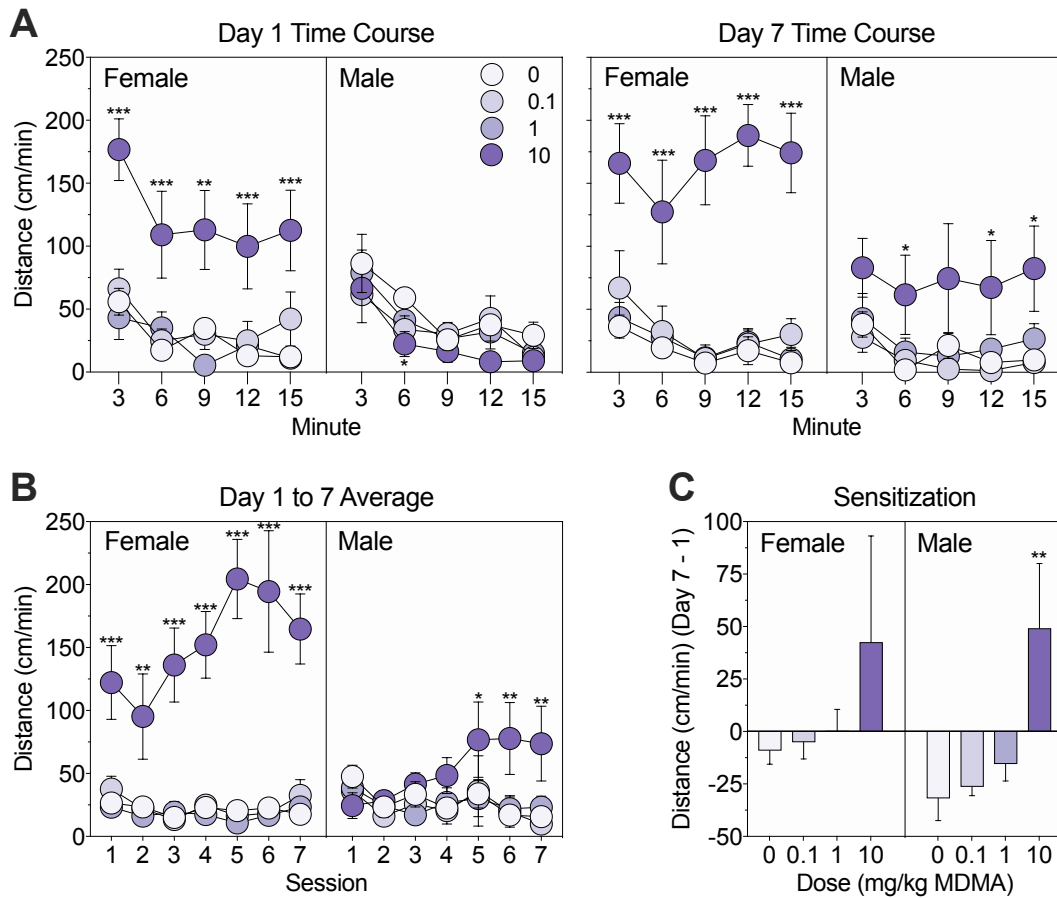
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### Supplementary Results

We found statistically significant sex differences in the effects of MDMA on locomotor activity during training. There was a main effect of sex that trended towards significance [ $F(1, 37) = 3.06, p = 0.09$ ] and a significant group-by-sex interaction [ $F(3, 37) = 9.99, p < 0.001$ ] on Day 1 (**Supplementary Figure 1A, left**). There was also a significant main effect of sex [ $F(1, 37) = 5.76, p = 0.02$ ] and a significant group-by-sex interaction [ $F(3, 37) = 3.27, p = 0.03$ ] on Day 7 (**Supplementary Figure 1A, right**). Sex differences were observed only in mice receiving 10 mg/kg MDMA (Day 1:  $p < 0.001$ , all other  $p$  values  $> 0.2$ ; Day 7:  $p < 0.001$ , all other  $p$  values  $> 0.3$ ). Compared to saline controls of the same sex, female ( $p < 0.001$ ) but not male ( $p = 0.17$ ) mice receiving 10 mg/kg MDMA showed significantly increased locomotion on Day 1, and both female ( $p < 0.001$ ) and male ( $p = 0.01$ ) mice receiving 10 mg/kg MDMA showed significantly increased locomotion on Day 7.

There was also a significant main effect of sex [ $F(1, 37) = 7.61, p = 0.009$ ] and a significant group by-sex interaction [ $F(3, 37) = 11.8, p < 0.001$ ] on average daily locomotion across the seven days of training (**Supplementary Figure 1B**). Sex differences were observed only in mice receiving 10 mg/kg MDMA ( $p < 0.001$ ; all other  $p$  values  $> 0.6$ ). Compared to saline controls of the same sex, female ( $p < 0.001$ ) but not male ( $p = 0.09$ ) mice receiving 10 mg/kg MDMA showed significantly increased locomotion across the seven days of training. In female mice, there was a significant main effect of group [ $F(3, 17) = 39.12, p < 0.001$ ] and a significant group-by-day interaction [ $F(18, 102) = 2.07, p = 0.01$ ]. Compared to female saline controls, only female mice receiving 10 mg/kg showed significantly increased locomotion ( $p < 0.001$ ; all other  $p$  values  $> 0.8$ ) and this effect was observed on all seven days of training ( $p$  values  $\leq 0.002$ ). In male mice, there was no significant main effect of group [ $F(3, 20) = 1.63, p = 0.21$ ] but there was a significant group-by-day interaction [ $F(18, 120) = 2.02, p = 0.01$ ]. Compared to male saline controls, only male mice receiving 10 mg/kg showed significantly increased locomotion on the last three days ( $p$  values  $\leq 0.04$ ) but not the first four days ( $p$  values  $> 0.2$ ) of training. Despite significant sex differences in the acute effects of MDMA on locomotion, no main effect of sex [ $F(1, 37) = 0.71, p = 0.41$ ] or group-by-sex interaction [ $F(3, 37) = 0.19, p = 0.9$ ] was observed for the development of sensitization as measured by the difference in average locomotion on Day 7 versus Day 1 (**Supplementary Figure 1C**).



**Supplementary Figure 1 Sex differences in effects of MDMA on locomotion.** Data from Figure 2 divided by female (**left**) and male (**right**) mice. **(A)** Time course of locomotion on Day 1 (**left**) and Day 7 (**right**) of training. Female mice receiving 10 mg/kg MDMA exhibited increased locomotion relative to female saline controls on Days 1 and 7. Male mice receiving 10 mg/kg MDMA exhibited increased locomotion relative to male saline controls on Day 7 only. **(B)** Average locomotion on each of the seven days of training. Female mice receiving 10 mg/kg MDMA exhibited increased locomotion relative to female saline controls on all seven days. Male mice receiving 10 mg/kg MDMA exhibited increased locomotion relative to male saline controls from Day 5 to Day 7 only. **(C)** Development of sensitization as measured by the difference in average locomotion on Day 7 versus Day 1. There was no main effect of sex or group-by-sex interaction. Asterisks identify significant comparisons against the saline control group of the same sex and at the same time point.