

Cannabidiol ameliorates emotional and cognitive deficits induced by acute and prolonged alprazolam exposure in adult mice: evidence for sex-specific therapeutic responses

F. Navarrete^{1,2,3}, A. B. Torregrosa^{1,2,3}, J. Manzanares^{1,2,3} †

1. Instituto de Neurociencias, Universidad Miguel Hernández-CSIC. San Juan de Alicante, Spain.
2. Red de Investigación en Atención Primaria de Adicciones (RIAPAd), Instituto de Salud Carlos III. Madrid, Spain.
3. Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL). Alicante, Spain.

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1. OBJECTIVES

- To determine whether CBD (10, 20 and 40 mg/kg, i.p.) reverses the cognitive impairments induced by acute APZ administration (0.5 mg/kg, i.p.) in male and female adult CD1 mice.
- To evaluate whether CBD (20 and 40 mg/kg, i.p.) modulates the emotional and cognitive alterations induced by prolonged APZ administration (0.5 mg/kg/day, i.p.) in male and female adult CD1 mice.

2. EFFECTS OF CANNABIDIOL ON ACUTE ALPRAZOLAM-INDUCED COGNITIVE IMPAIRMENTS

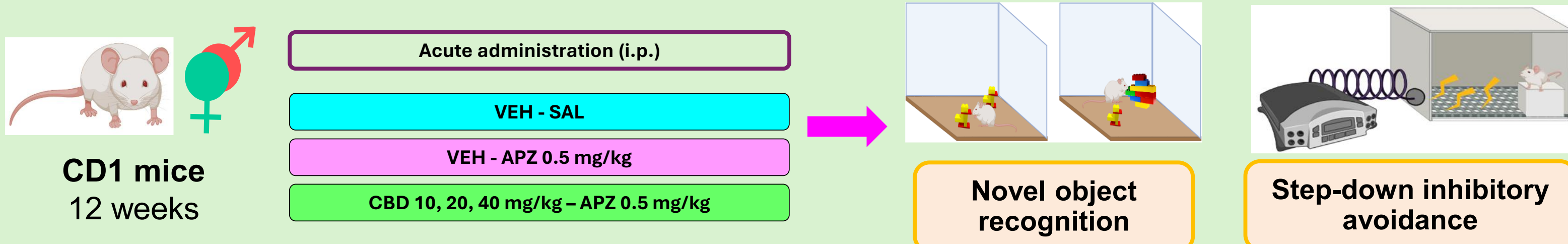


Figure 1. Timeline diagram of the experimental procedure used for the evaluation of cannabidiol (CBD) acute effects on cognitive impairments induced by acute APZ administration evaluated by the novel object recognition (NOR) and step-down inhibitory avoidance (SDIA) tests in male and female CD1 adult mice (12 weeks). APZ administration (0.5 mg/kg, i.p.) was performed acutely 30 min before behavioral evaluation, and CBD (10, 20 and 40 mg/kg, i.p.) was injected 90 min prior APZ administration.

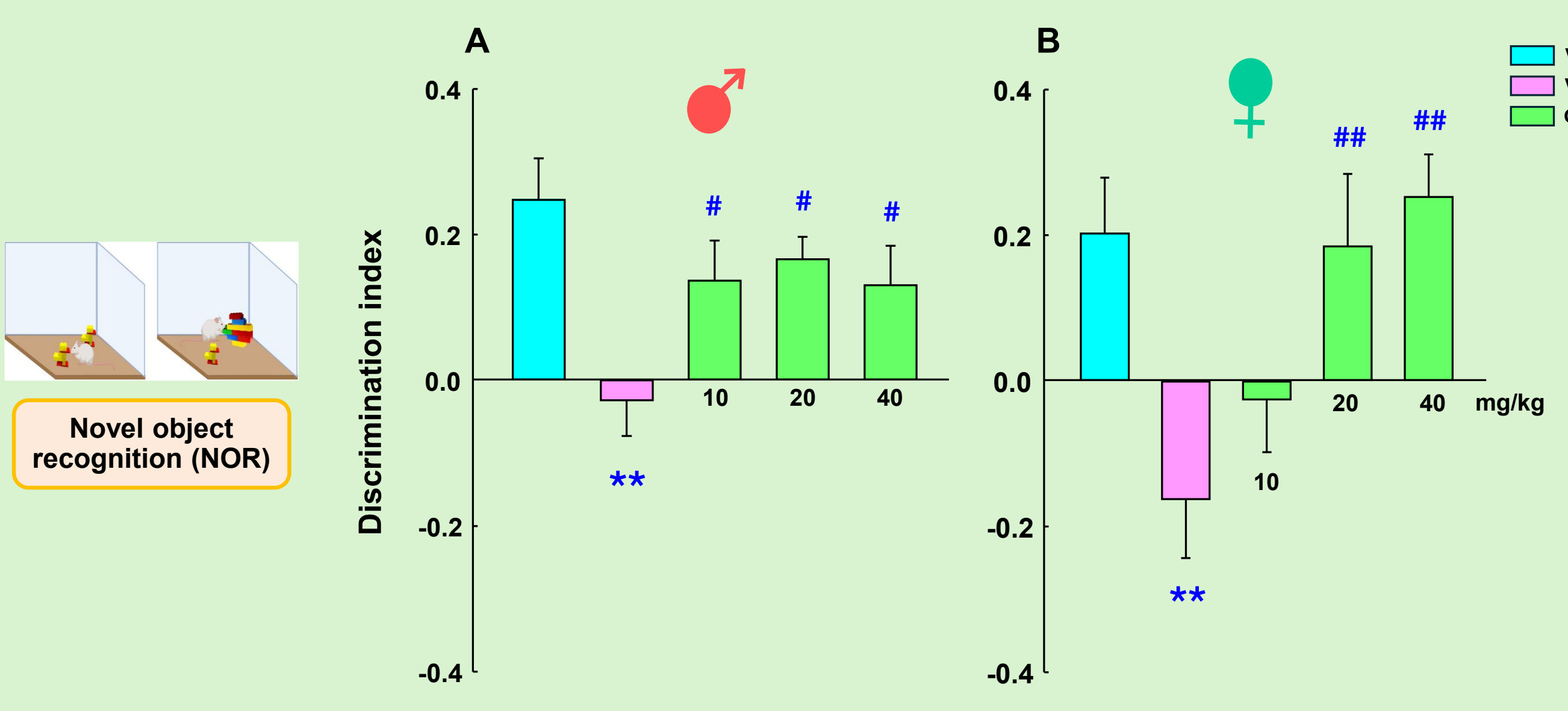


Figure 2. Evaluation of CBD effects on acute APZ-induced alterations on recognition memory in male (A) and female (B) adult CD1 mice measured by the novel object recognition (NOR) paradigm. ** p<0.01 vs VEH-SAL groups; # p<0.05, ## p<0.01 vs VEH-APZ groups.

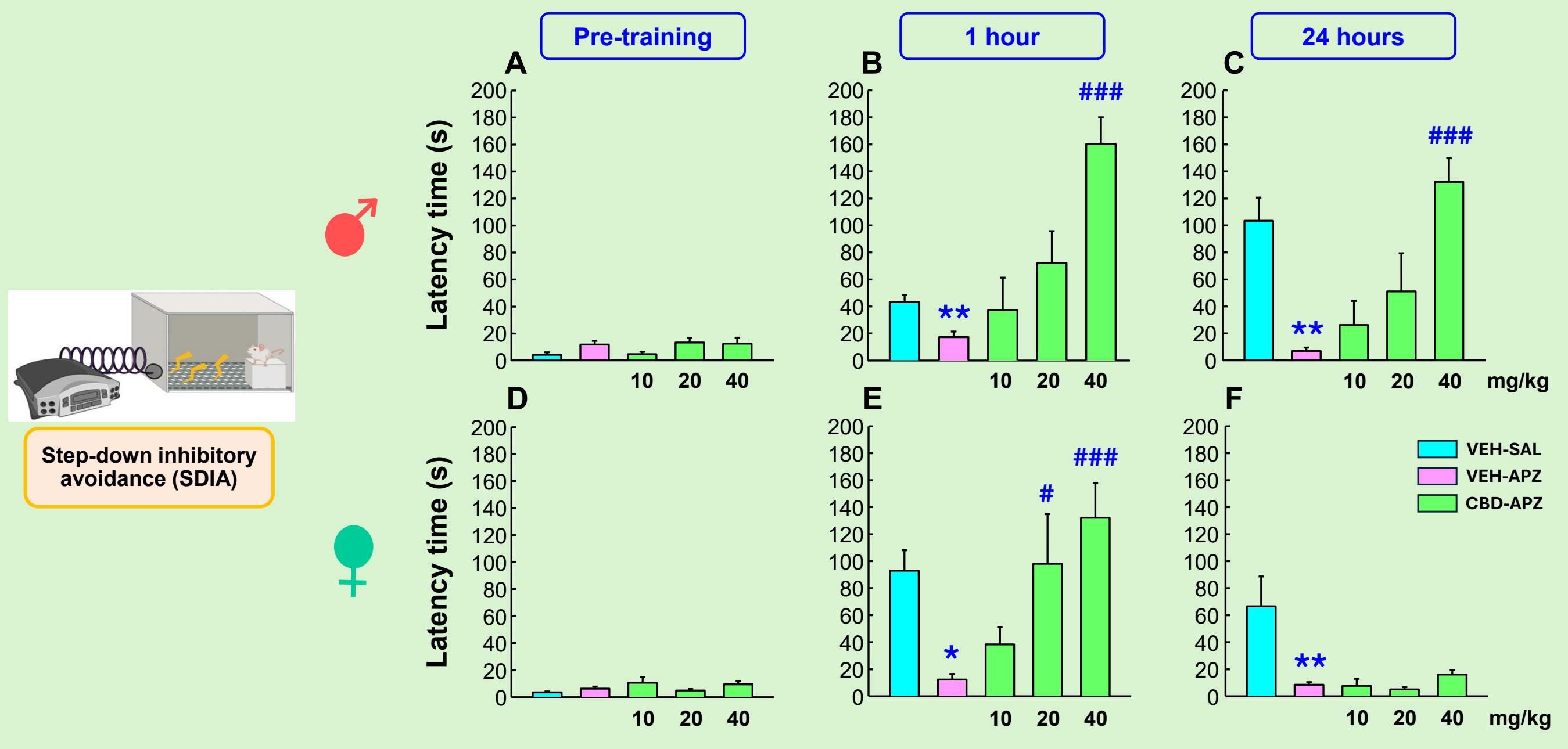


Figure 3. Evaluation of CBD effects on acute APZ-induced alterations on aversive short- and long-term memory in male (A, B, C) and female (D, E, F) adult CD1 mice measured by the step-down inhibitory avoidance (SDIA) paradigm. * p<0.05, ** p<0.01 vs VEH-SAL groups; # p<0.05, ### p<0.001 vs VEH-APZ groups.

3. EFFECTS OF CANNABIDIOL ON EMOTIONAL AND COGNITIVE ALTERATIONS INDUCED BY PROLONGED ALPRAZOLAM EXPOSURE

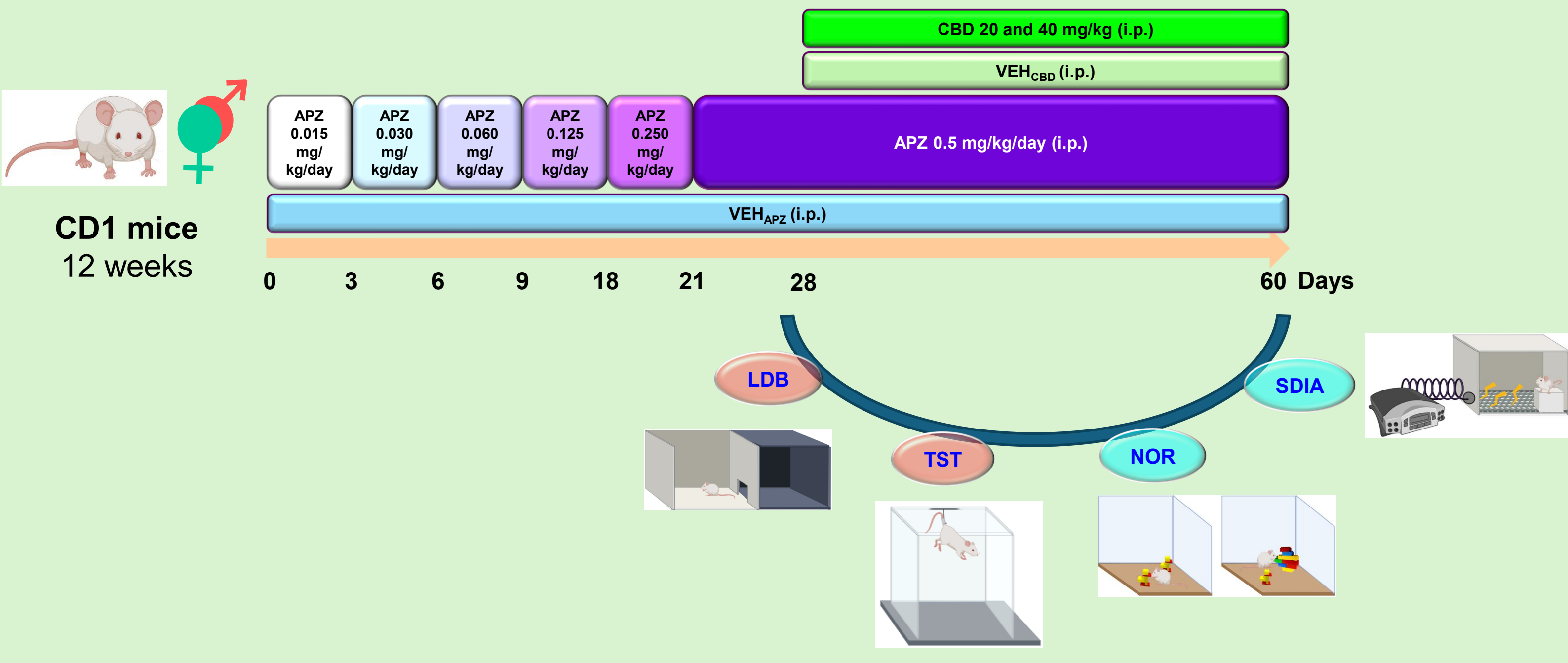


Figure 4. Timeline diagram of the experimental procedure used to evaluate the effects of cannabidiol (CBD) on emotional and cognitive impairments induced by prolonged alprazolam (APZ) administration in male and female adult CD1 mice (12 weeks old). Emotional and cognitive function were assessed using the light–dark box (LDB), tail suspension test (TST), novel object recognition (NOR), and step-down inhibitory avoidance (SDIA) tests. The APZ dose was progressively increased from 0.015 to 0.5 mg/kg/day (administered twice daily, i.p.), while CBD was administered from days 28 to 60 at doses of 20 or 40 mg/kg (twice daily, i.p.).

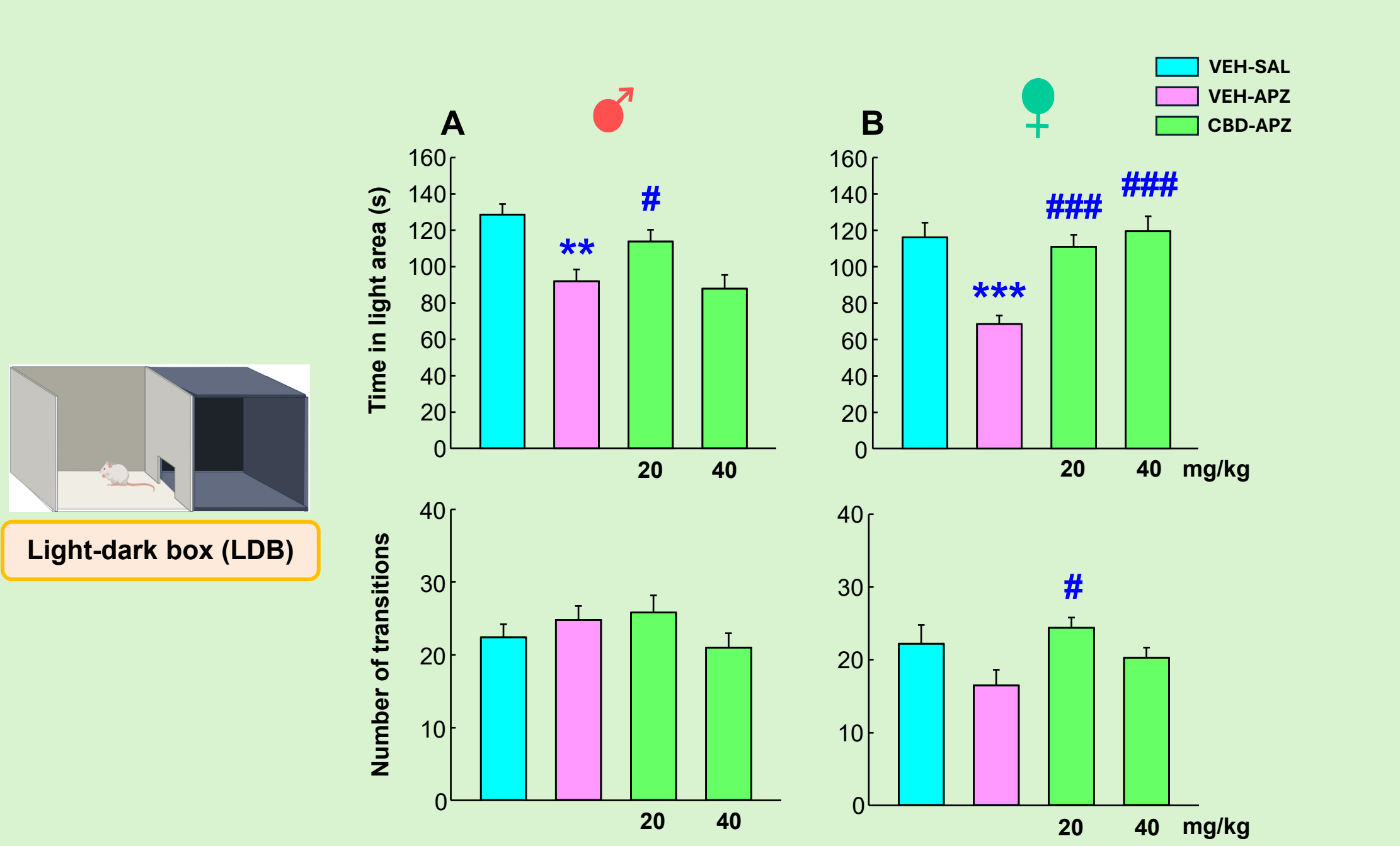


Figure 5. Evaluation of CBD effects on prolonged APZ-induced alterations on anxiety-like behavior in male (A) and female (B) adult CD1 mice measured by the light-dark box (LDB) test. ** p<0.01, *** p<0.001 vs VEH-SAL groups; # p<0.05, ### p<0.001 vs VEH-APZ groups.

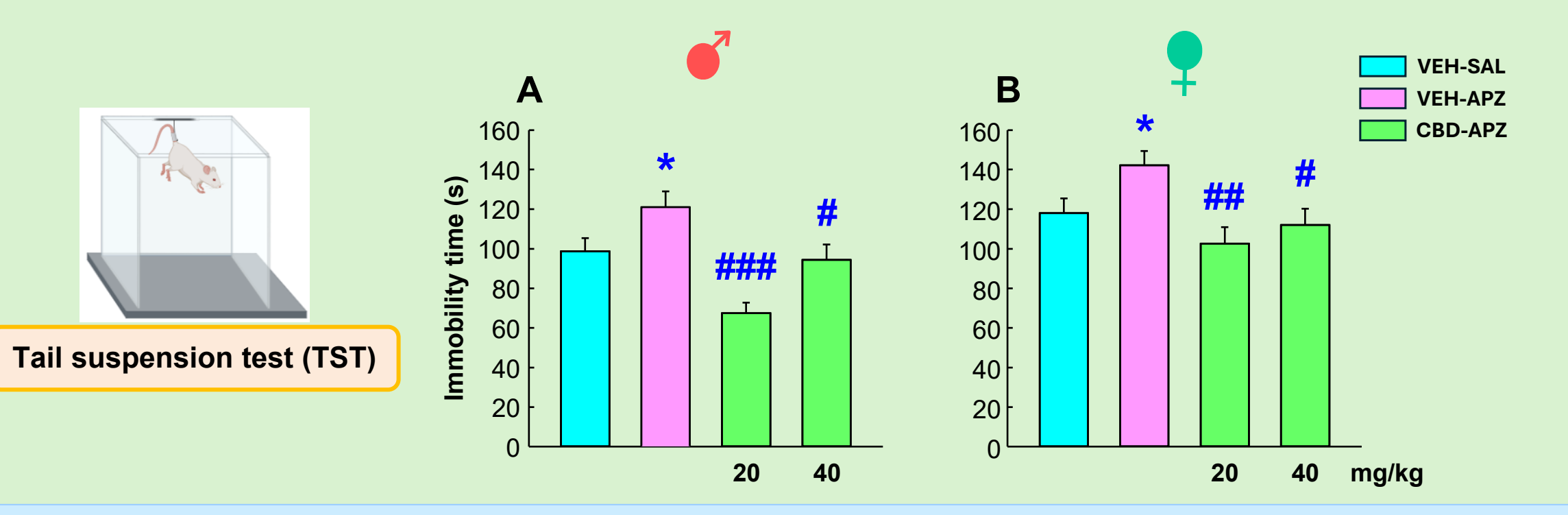


Figure 6. Evaluation of CBD effects on prolonged APZ-induced alterations on depressive-like behavior in male (A) and female (B) adult CD1 mice measured by the tail suspension test (TST). * p<0.05 vs VEH-SAL groups; # p<0.05, ## p<0.01, ### p<0.001 vs VEH-APZ groups.

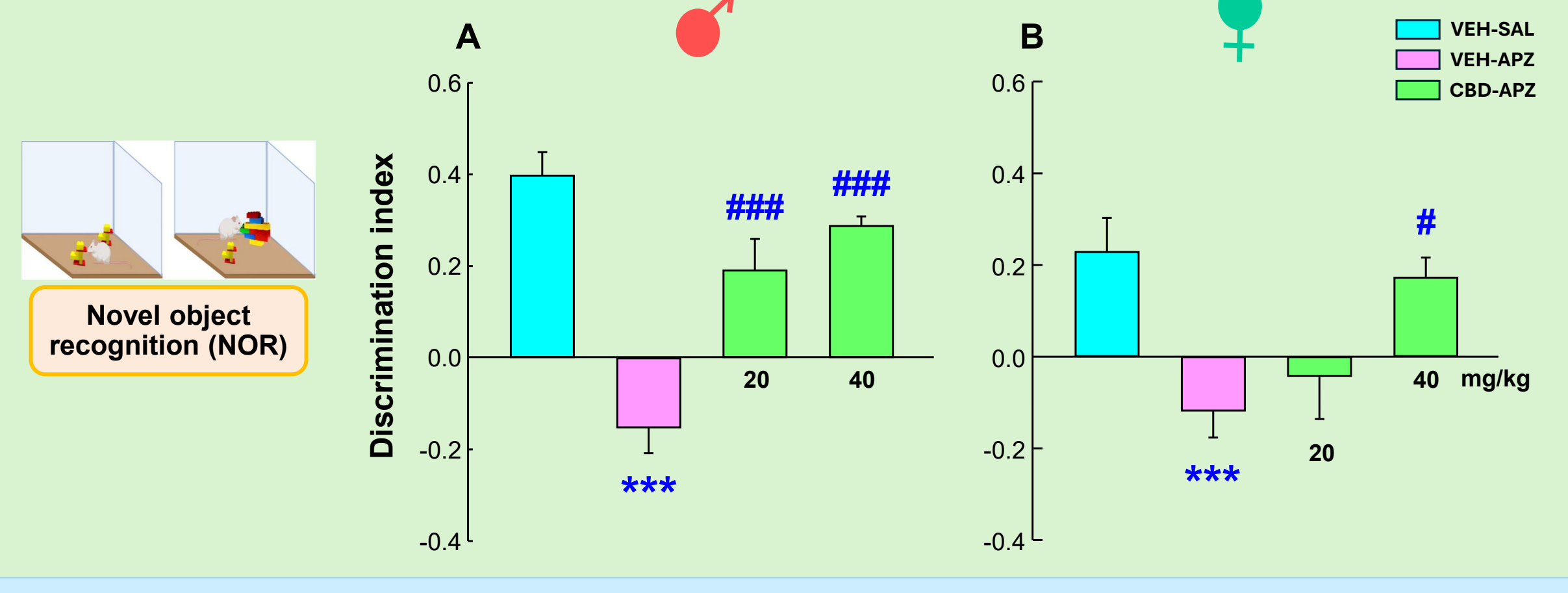


Figure 7. Evaluation of CBD effects on prolonged APZ-induced alterations on recognition memory in male (A) and female (B) adult CD1 mice measured by the novel object recognition (NOR) paradigm. *** p<0.001 vs VEH-SAL groups; # p<0.05, ### p<0.001 vs VEH-APZ groups.

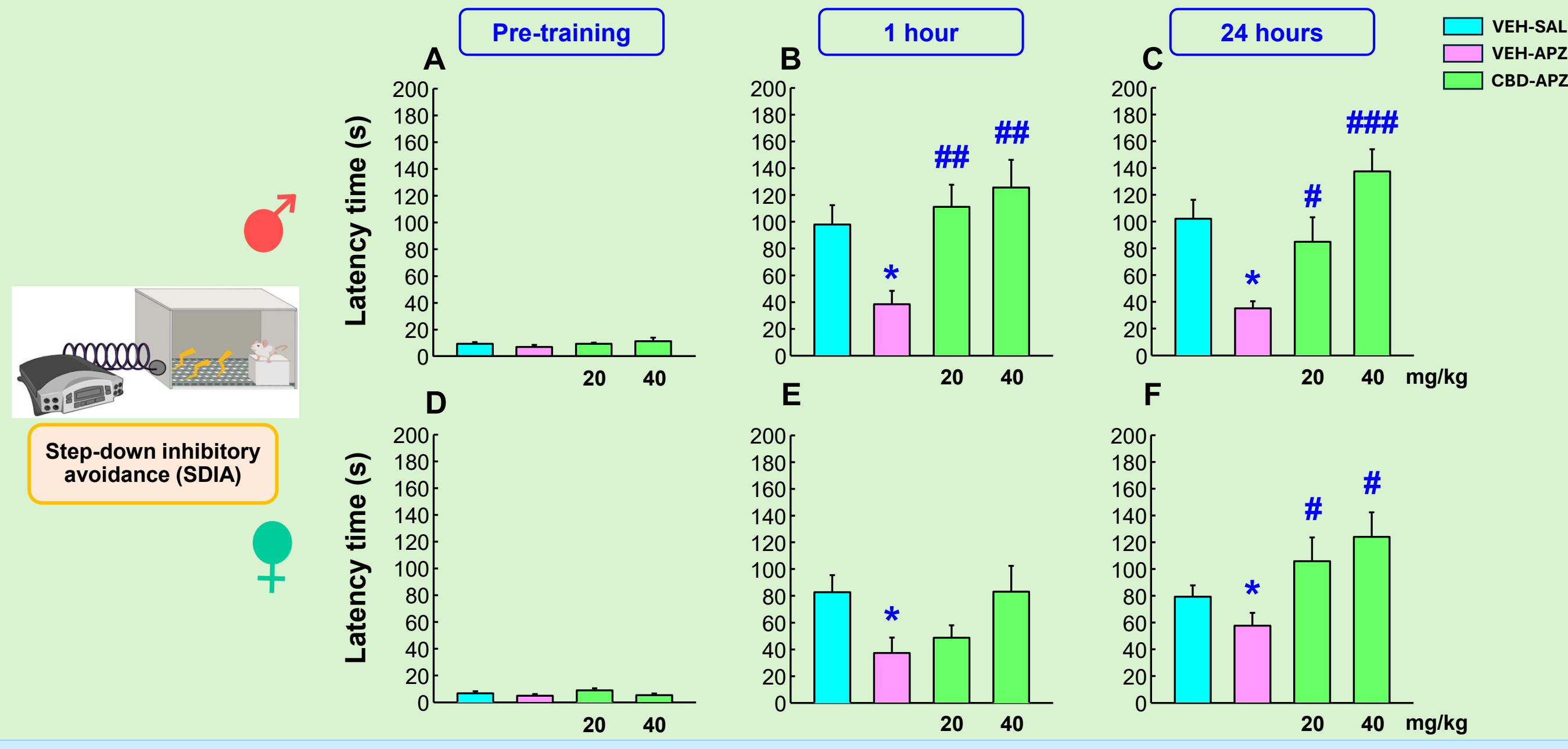


Figure 8. Evaluation of CBD effects on prolonged APZ-induced alterations on aversive memory in male (A, B, C) and female (D, E, F) adult CD1 mice measured by the step-down inhibitory avoidance (SDIA) paradigm. * p<0.05 vs VEH-SAL groups; # p<0.05, ## p<0.01, ### p<0.001 vs VEH-APZ groups.

4. CONCLUSIONS

- CBD attenuates alprazolam-induced emotional and cognitive impairments, with effects dependent on sex and behavioral domain.
- CBD may represent a promising adjunctive strategy to mitigate the neurobehavioral consequences of long-term benzodiazepine exposure.
- Sex-specific responses should be considered in future translational and personalized therapeutic approaches to benzodiazepine dependence and withdrawal.

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All authors state that they have no potential conflicts of interest.