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### Assessment of Oxytocin-Receptor Modulation of Social Recognition Following Adolescent Ethanol Exposure

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## Introduction

### Adolescent Intermittent Ethanol (AIE):

- Previous studies have indicated that AIE during postnatal(P) day 25-45 have resulted in greater behavioral changes, deficits in executive functioning and affective responses.

### Oxytocin (OXT):

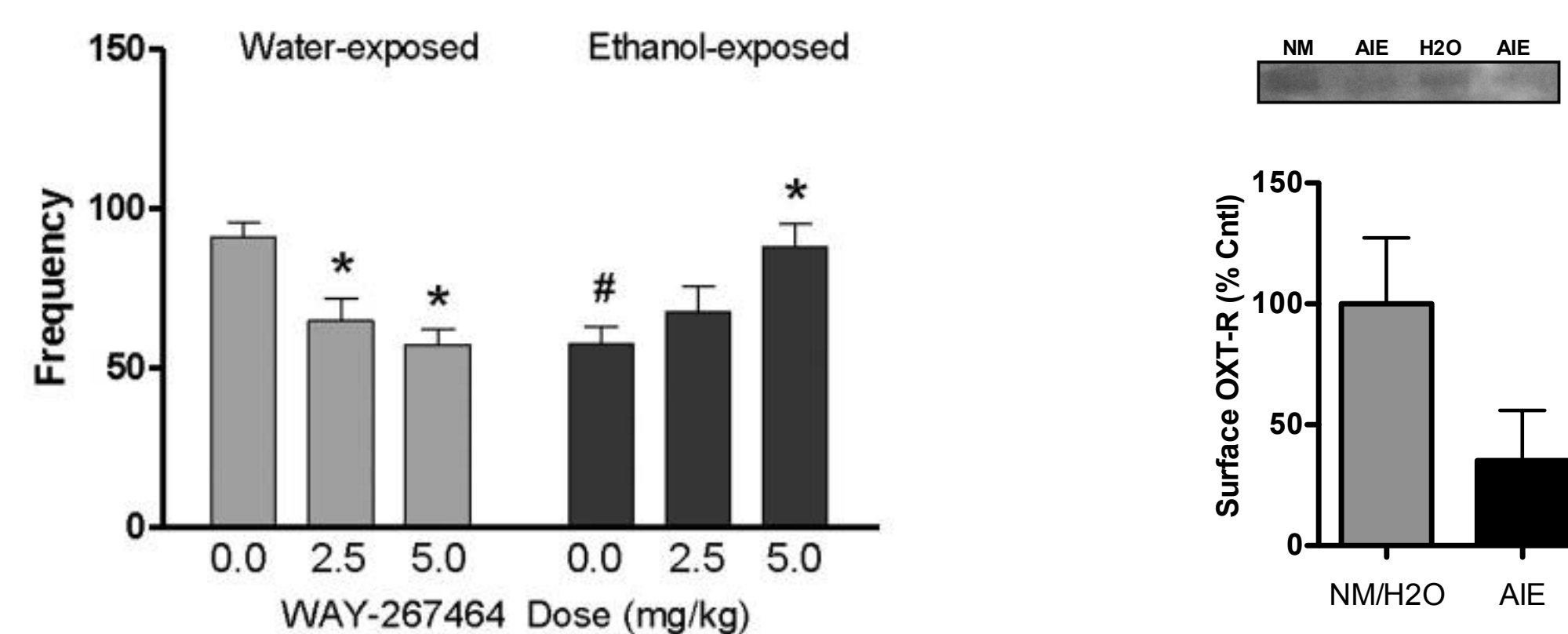
- OXT is involved in mating, social bonding, and innervates brain regions such as the nucleus accumbens, lateral septum, and the prefrontal cortex
- Previous studies assessing OXT indicated that low doses enhance social recognition in male rats.
- AIE resulted in changes in OXT receptor surface expression in the hypothalamus.
- Human OXT research has demonstrated subtle effects of OXT on social cognition and behavior.

### WAY 267,464 (WAY):

- Synthetic oxytocin-receptor non-peptide agonist
- WAY has shown to have similar modulation as OXT

### Social Recognition Test

- Brain regions mediated by social recognition include hippocampus, prefrontal cortex, nucleus accumbens and amygdala
- Tests non-spatial, short term memory in rodents and adolescent ethanol exposure impairs recognition

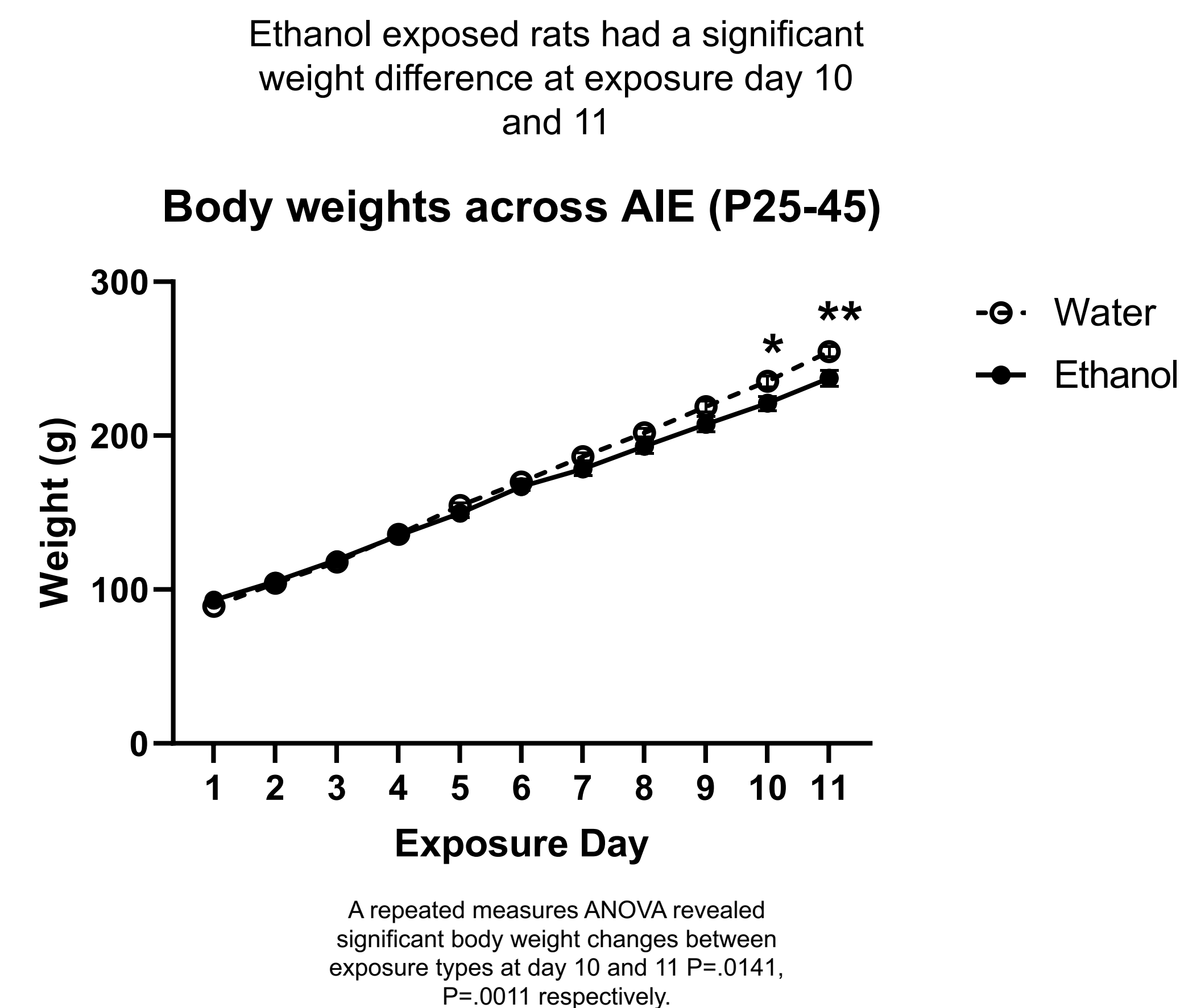


## Purpose

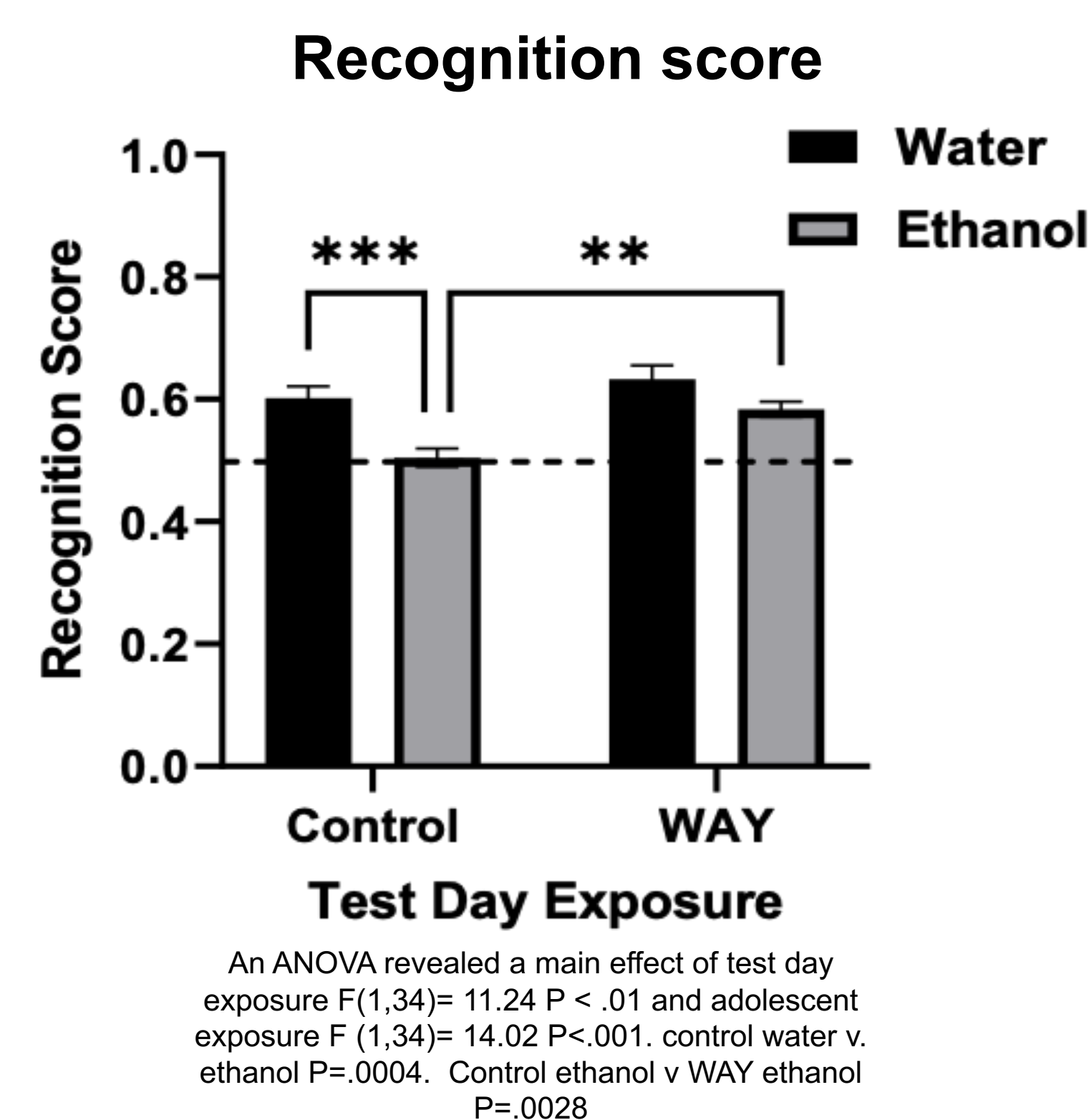
The current study assessed if administration of the selective non-peptide OXT receptor agonist WAY 267464 (WAY) modulates social recognition and reverses the social recognition deficits resulting from AIE in male rats.

## Methods

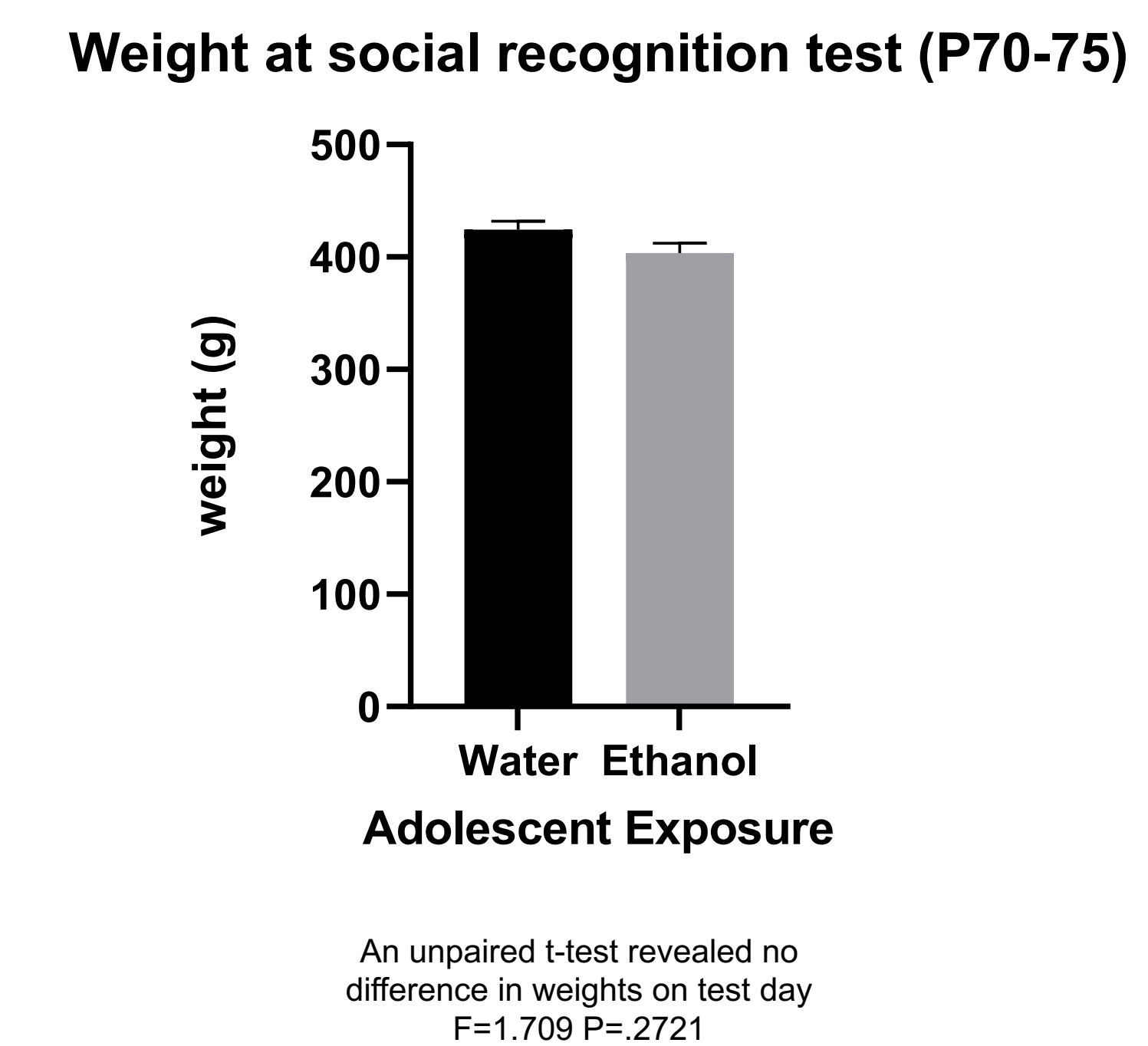
- **Experimental Subjects:**
  - 38 male Sprague Dawley rats were used, divided into 4 treatment group. Adolescent exposure of water or AIE and test day exposure of WAY or vehicle. (n=9-10/group) A total of 60 juvenile rats P24-30 used for social recognition.
- **Housing:**
  - Housed in pairs 2/cage or groups 3/cage.
- **Exposure:**
  - Either ethanol (4.0 g/kg, 25% v/v) (AIE) or an equivalent volume of tap water (water) given intragastrically (i.g.) every other day (P25-P45), resulting in 11 total intubations
  - Animals then sat undisturbed for ~25 days
- **WAY effects on social recognition:**
  - On P70-75 animals were injected intraperitoneally (i.p) at a volume of 2 ml/kg a 5mg/kg of synthetic oxytocin-receptor non-peptide agonist (WAY) dissolved in 15% DMSO 2% tween80 and 83% physiological saline.
  - Placed immediately in the social recognition test cage.
- **Social Interaction Test:**
  - A large open cage with bedding was used for the recognition test
  - Experimental rats were isolate 24 hours prior to testing
  - Subject animals were given a 30 min. habituation period in the cage alone after exposure to WAY or control.
  - For testing, two 5-minute trials separated by an inter exposure period (30 min) .
    - Trial 1: male juvenile rat P24-30 is placed into cage for 5-minute interaction period
    - Trial 2: after 30 minutes, now familiar juvenile is placed back into cage along with a novel juvenile rat for a second 5-minute interaction period.
  - Trials were video recorded and assessed for interaction in seconds
  - **Social investigation:** (nosing, sniffing, grooming, or pawing)
  - **Interaction time of trial 1:** total time in seconds
  - **Recognition test of trial 2:** interaction with novel juvenile(s) / interaction with both juveniles (s))
  - **Impaired recognition-equivalent amount of investigation results in no recognition (less than .5)**
  - **Rodents' natural propensity is to explore novel objects.**
  - 30 minutes following the social recognition test rats were decapitated and brains were preserved for further research.



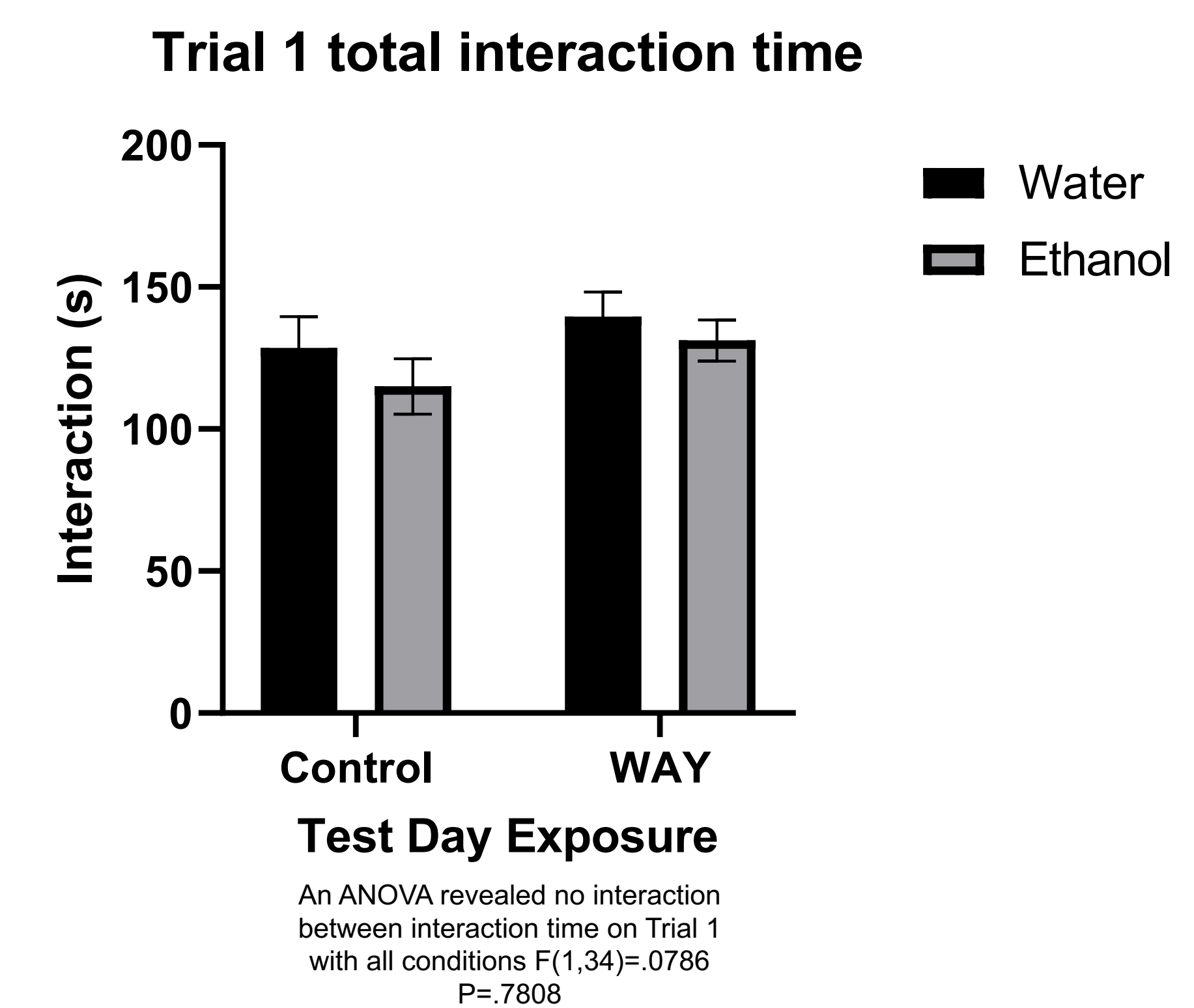
AIE adolescent exposure show deficit in social recognition and administration of WAY recovered the deficit



Weight change recovered by social recognition test



Trial 1 interaction time showed no difference in investigation across conditions



## Discussion

- Consistent with prior findings current results revealed social recognition deficits after exposure to AIE in male Sprague Dawley rats.
  - Previous research has looked at expression of the hypothalamus as a potential contributor to the behavioral deficits present. However, further investigation is needed to see if similar affects are evident during the social recognition test.
- AIE deficits were reversed by administration of OXT non-peptide agonist WAY-267464.
  - During trial 2 of the social recognition test, improvement of recognition was observed due to increased investigation of novel juvenile compared to the familiar juvenile.
  - After injection of 5mg/kg WAY AIE rats increased recognition. However, there was no difference after WAY injection in water exposed experimental rats.
- Trial 1 suggests there was no difference in investigation time of the juvenile across exposure groups.
  - This provides insight on how the experimental rats reacted to the novel juvenile.
  - The same amount of investigation suggests that deficits were not due to decreased interaction with the juvenile.
- Throughout AIE body weights stayed consistent until the final two days of exposure.
  - This is consistent with previous AIE designed experiments
- However, body weights recovered and were not different by the social recognition test day.
  - Importantly, body weights recovered after AIE suggesting that difference in investigation time was not due to alteration in body weight between adolescent exposure groups.

## Summary

- Social recognition deficits resulting from AIE were recovered after administration of WAY-267464.
- A main effect was revealed after AIE male rats were administered WAY-267464. Further investigation is needed to identify potential differences in brain region expression.

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