



Effects of fluoxetine on rodent cognition and behavior

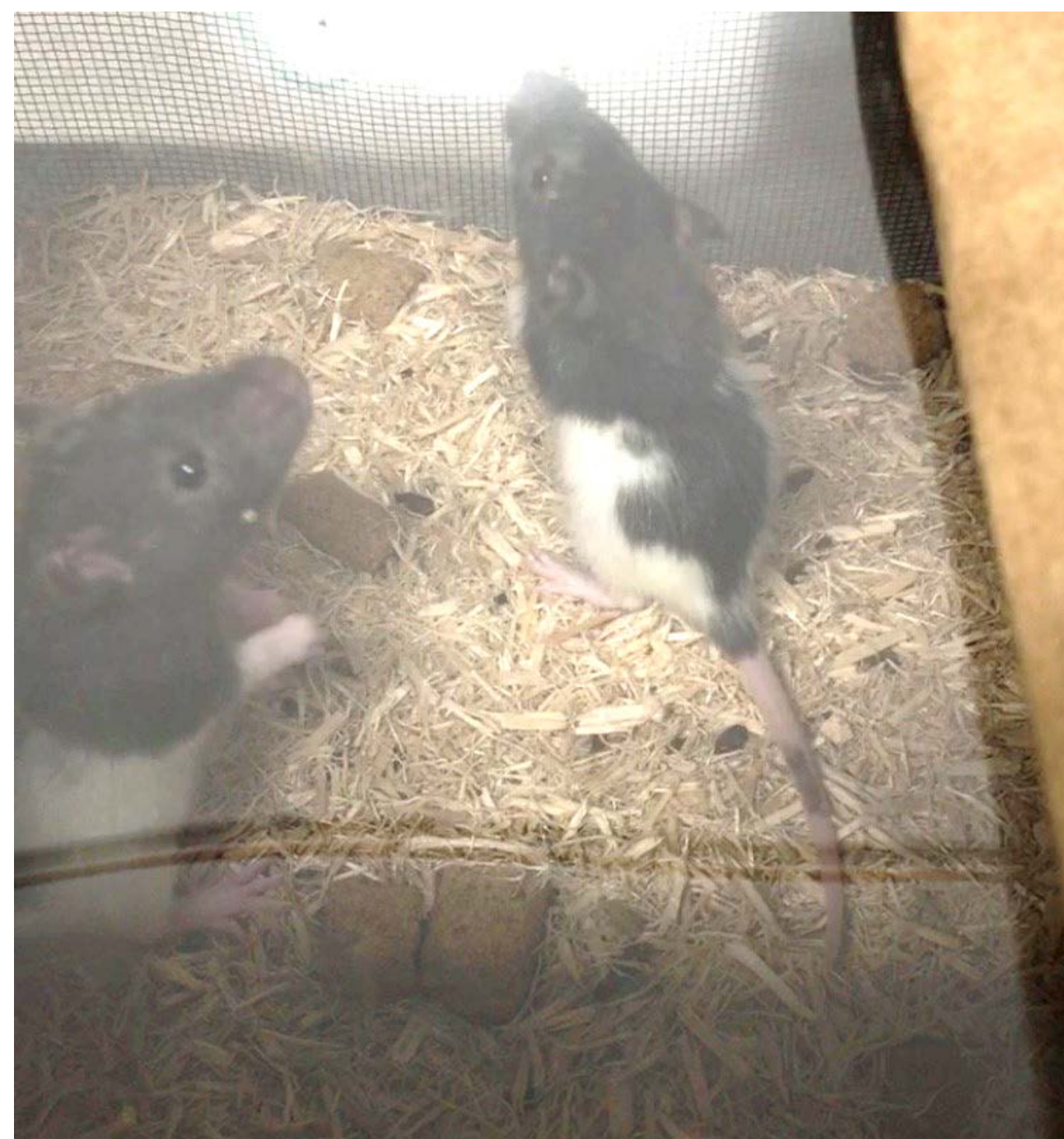


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Introduction

- Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) that has shown efficacy for treatment of depression in adolescents.
- However, enduring consequences for adolescent fluoxetine exposure is less well studied.
- We proposed to examine the effects of adolescent treatment vs adult treatment with fluoxetine (vs vehicle control) and examine the effects of drug administration on behavior and cognitive assessments during adulthood.

Subjects



These are adolescent rats at arrival in the lab (approximate age PND 23)

- Adolescent Long Evans rats (both male and female) were acquired from a commercial source (Envigo) and arrived at the laboratory at approximately postnatal day (PND) 23 after weaning.
- Subjects were group housed with free access to food and water and allowed to acclimate to the lab for about 1 week.
- Subjects were pair housed before experimental manipulations began.
- Cage mates were always in the same condition.

Experimental Design

	Fluoxetine	Vehicle
Adolescents	Fluox / Adol	Veh / Adol
Adults	Fluox / Adult*	Veh / Adult

Note: * indicates this group not completed

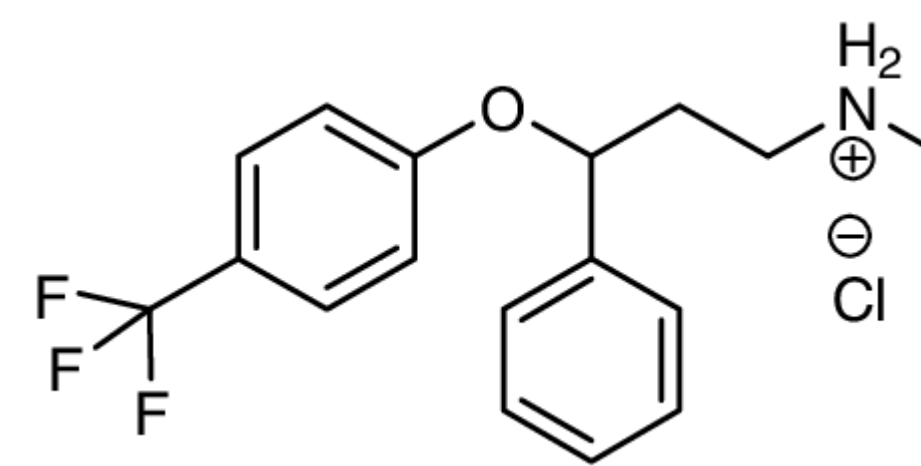
	ADOLESCENCE		ADULT TESTING
	ADOLESCENCE		ADULT TESTING
*		EARLY ADULTHOOD	ADULT TESTING
		EARLY ADULTHOOD	ADULT TESTING

Abstract

Recent epidemiological data suggest that approximately 8% of adolescent children are diagnosed with major depressive disorder. In addition, problems related to adolescent depression are well documented to continue into adulthood. Existing treatment regimens for adolescent major depressive disorder include both talk therapy and drug therapy using fluoxetine (Prozac), with fluoxetine being the only drug currently approved by the US Food and Drug Administration for the treatment of depression in adolescents. Yet long term effects of adolescent fluoxetine treatment have only recently begun to be studied. Given that central nervous system growth and maturation continues throughout adolescence and into early adulthood, the effects of fluoxetine treatment on developing neurocircuitry and behaviors is unclear. The goals of these experiments were to examine the long term effects of adolescent fluoxetine treatment and compare those data to adult animals treated with fluoxetine in a rodent model of behavior and cognition. Male and female rats that were obtained from commercial sources (Envigo) were used as subjects in these experiments. These experiments used a 2 (age) x 2 (drug treatment) factorial design, with about 10-12 animals in each of the 4 experimental groups (adolescent+fluoxetine; adolescent+vehicle; adult+fluoxetine; adult+vehicle). Animals were administered 10 mg/kg (ip) of fluoxetine hydrochloride (Toronto Research Chemicals), or vehicle, for 14 days either during adolescence or adulthood. Afterwards during adulthood, all animals experienced a series of behavioral and cognitive tasks that assessed locomotor behavior in an open field, memory for novel objects after a short delay period, and behavior in an elevated zero-maze, which is a well validated task to assess anxiety-like behavior. Our hypotheses were that fluoxetine treatment during adolescence, but not adulthood, would be more likely to impact those behaviors more closely related to symptoms observed during major depressive disorder (anxiety, cognition). Results and implications from our on-going data collection will be discussed.

Drugs

- Fluoxetine was purchased commercially (Toronto Research Chemicals).
- Subjects received daily ip injections of fluoxetine or saline vehicle in the home cage room.
- Injections were delivered at a volume of 1 ml/kg. Injections were delivered during adolescence or adulthood.
- After washout, animals were assessed in behavior and cognition tasks



Approximately one-half of the subjects received daily injections of fluoxetine, while the other half received saline vehicle injections on the same schedule.

Results

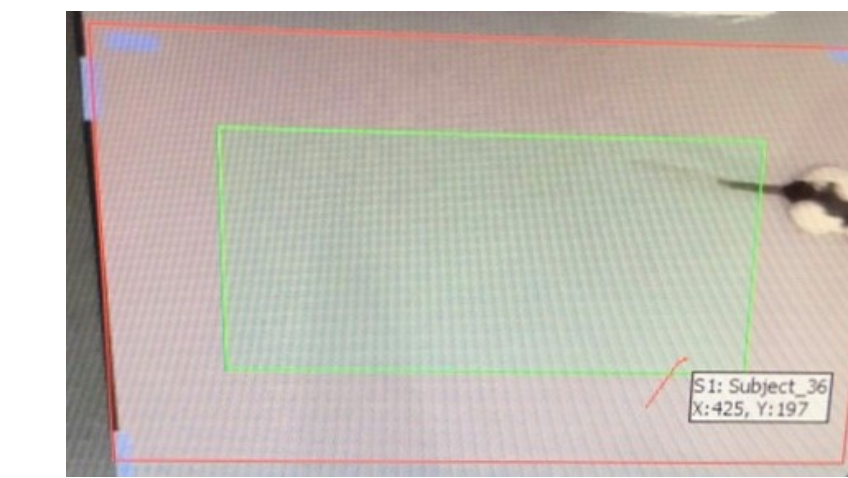


Figure 1. Open Field (exploratory behavior) Subjects explored the open field and total distance (cm) was recorded. Distance traveled by animals in each experimental group was comparable.

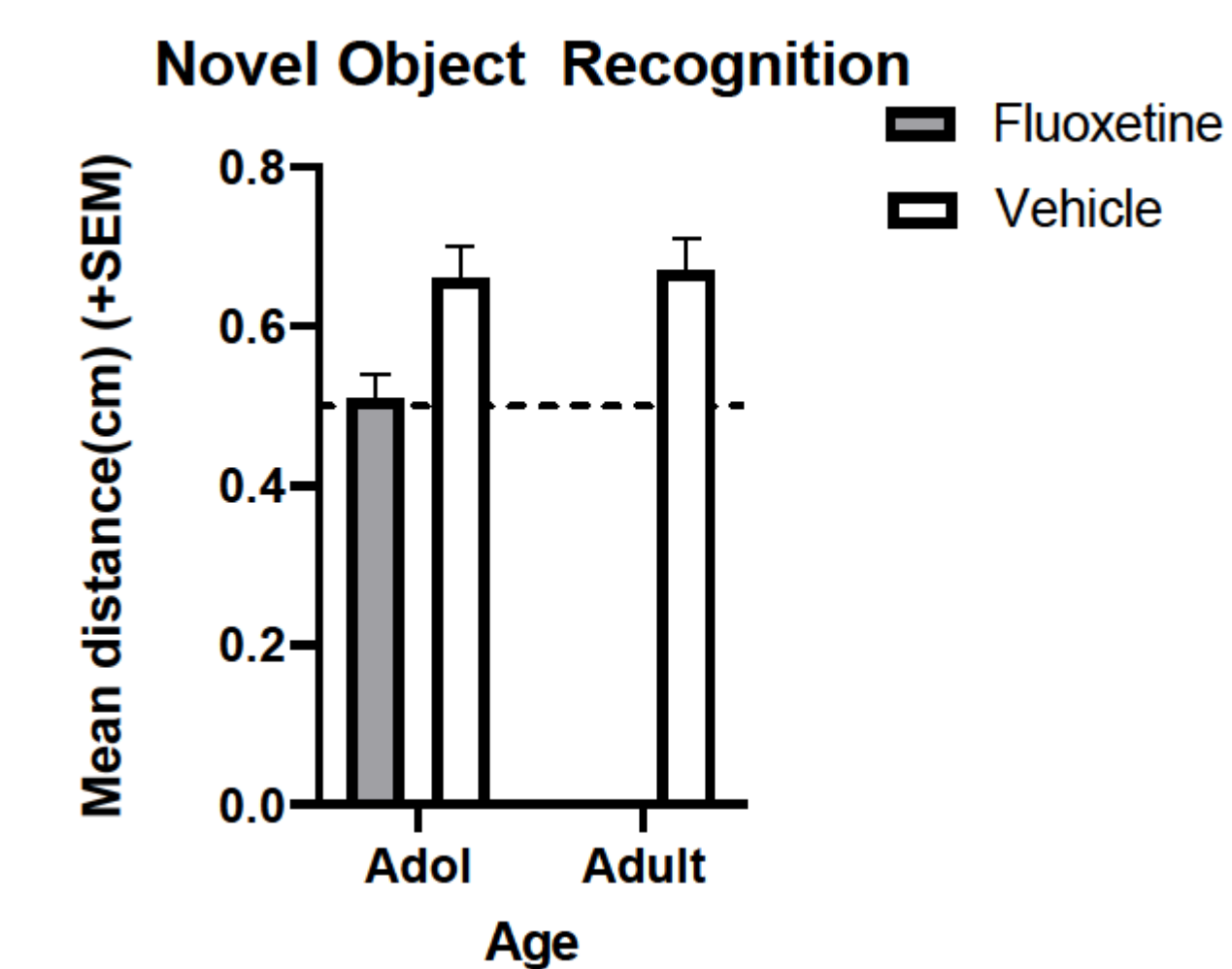
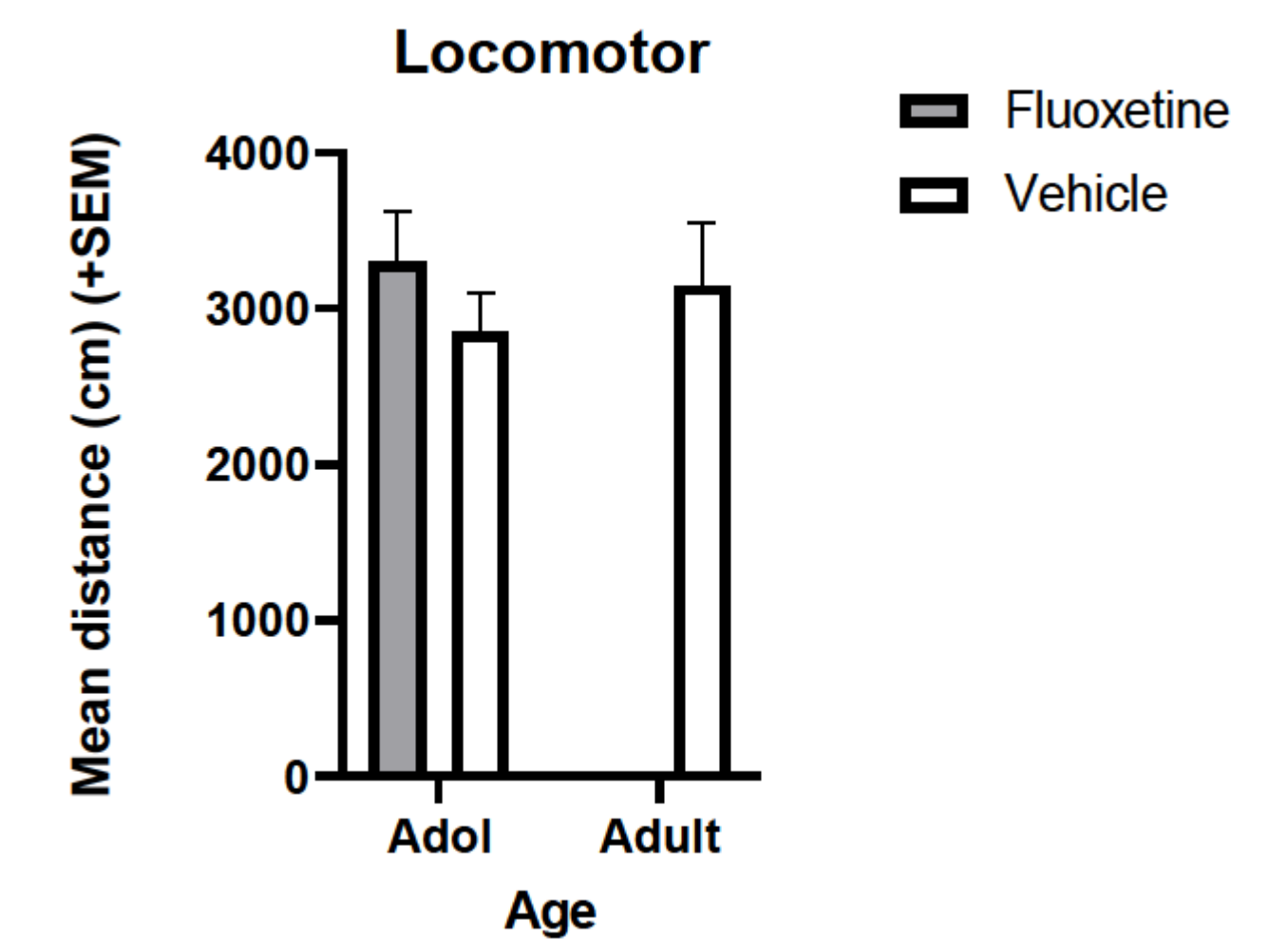
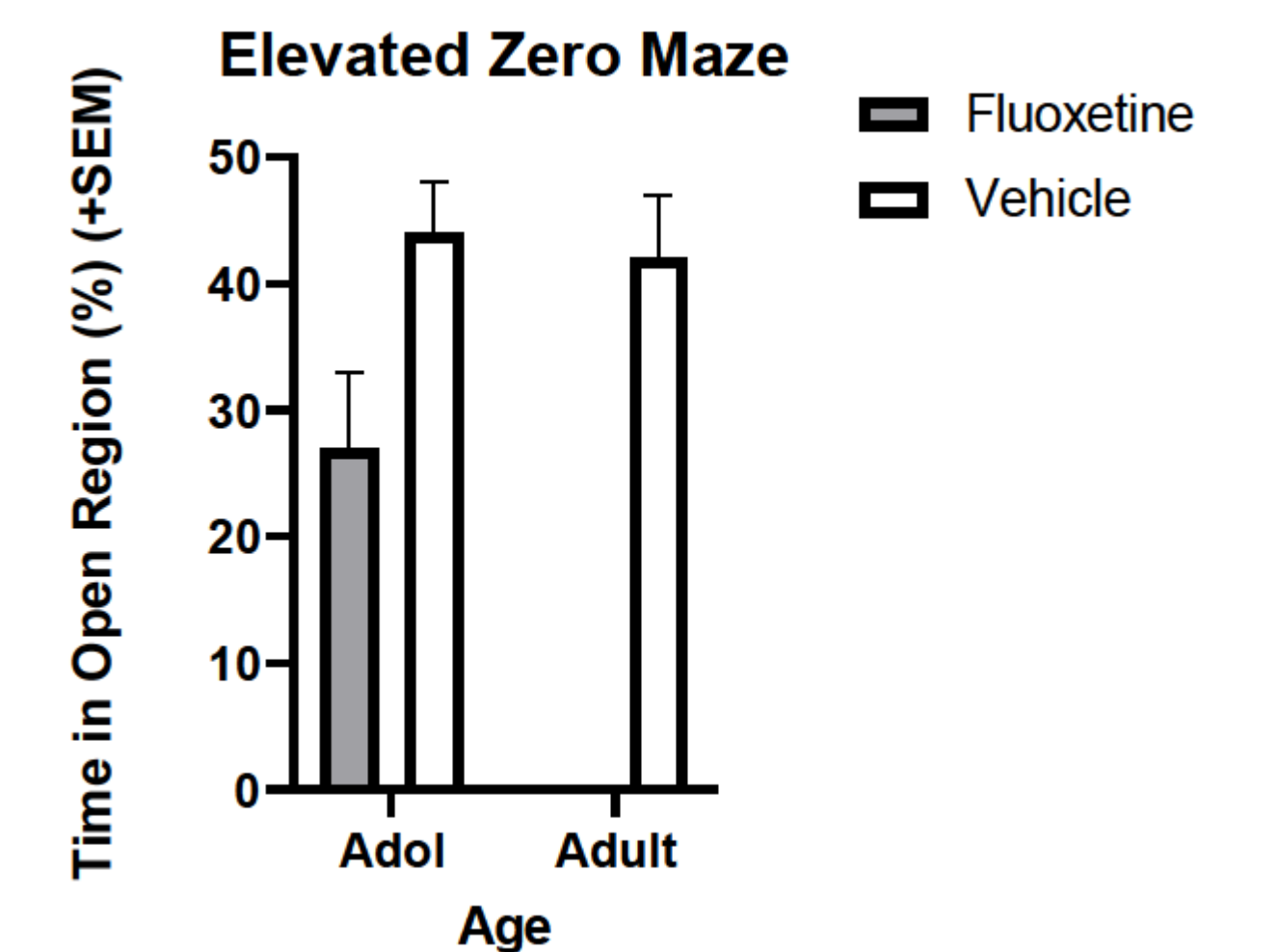


Figure 2. Novel Object Recognition (memory) The subjects who received drug during adolescence were impaired in their memory compared to control subjects.



Figure 3. Elevated Zero Maze (anxiety) Subjects who received drug during adolescence appeared to spend less time in the open regions (suggesting more anxiety-like behavior) compared to subjects receiving vehicle.



Conclusions & Implications

- There did not appear to be a significant effect of adolescent drug administration on exploratory behavior in an open field environment.
- However, in both the memory and anxiety assessments, animals that received fluoxetine during adolescence appeared to be impaired compared to the control animal counterparts.
- These experiments were unfortunately prematurely truncated due to external events.
- Completion of all subjects in all experiments at some future time point will hopefully permit a more full consideration of the data, evaluation of statistical significance, and implications for these data.

Acknowledgements:

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