# Environmental Enrichment Attenuates Nicotine Behavioral Sensitization in Male and Female Rats

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Environmental enrichment decreases nicotine reactivity in male rats, but these effects have not been examined in females. This research was conducted to examine the effects of enrichment on nicotine behavioral sensitization (i.e., nicotine reactivity) in male and female rats. One hundred forty-four Sprague–Dawley rats (72 male, 72 female) were raised in isolation, social enrichment (groups of three rats [SE]), or combined physical enrichment and social enrichment (groups of three rats with novel toys [PESE]) housing conditions. As adults, they received daily subcutaneous injections of saline or nicotine (0.1, 0.5, or 1.0 mg/kg) for 12 days; locomotor activity was measured on drug days 1, 5, 9, and 12. Before drug administration, PESE and SE decreased activity in males; only PESE decreased activity in females, F(2, 120) = 6.51, p < .01. In the drug phase, nicotine behavioral sensitization occurred, F(8.46, 6)341.04) = 20.71, p < .001, and was greater in females than males, F(8.340, 319.715) = 2.072, p < .05. Enrichment decreased nicotine behavioral sensitization in both sexes, F(16.91, 341.04) = 2.48, p < .01. In conclusion, nicotine behavioral sensitization occurred in male and female rats and was attenuated by environmental enrichment. This research has implications for treatment and prevention strategies in humans. Programs that incorporate aspects of social and environmental stimulation may have enhanced effectiveness in preventing and reducing cigarette smoking and may have implications for relapse prevention.

Keywords: environmental enrichment, nicotine reactivity, nicotine behavioral sensitization, males, females

Cigarette smoking is the leading cause of preventable death in the United States (Centers for Disease Control, 2012) and is influenced by social and environmental factors (Brunner, Shipley, Blane, Smith, & Marmot, 1999; Gilman, Abrams, & Buka, 2003; Harwood, Salsberry, Ferketich, & Wewers, 2007). It is possible that social and environmental factors contribute to smoking behavior by altering reactivity to nicotine, the addictive chemical found in all tobacco products (Jarvik, Cullen, Gritz, Vogt, & West, 1977), and nicotine reactivity may underlie smoking initiation. Research with male rat models indicates that social and environmental factors cause changes in the brain that affect nicotine behavioral sensitization, an index of nicotine reactivity, as well as

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other actions of nicotine (Coolon & Cain, 2009; Green, Cain, Thompson, & Bardo, 2003; Zhu, Bardo, Green, Wedlund, & Dwoskin, 2007). Following from this research, smoking treatment and prevention strategies that incorporate social and environmental components may be particularly effective to reduce cigarette smoking. However, there is no research examining the effects of environmental enrichment (EE) on nicotine reactivity in female rats. The global rise of smoking in women and the lack of research examining effects of disadvantage and socioeconomic status (SES) on women's risk of tobacco use (Amos, Greaves, Nichter, & Bloch, 2012) are compelling reasons to include females in all studies of factors affecting tobacco use. Given the valuable implications of this line of research for public health, it is imperative to determine whether EE reduces nicotine reactivity in female rat models. In this research, effects of EE on nicotine reactivity were examined in female and male rats.

Nicotine behavioral sensitization indexes nicotine reactivity in rats. Nicotine behavioral sensitization is a progressive and incremental increase in nicotine's effects, including locomotion, that occurs in response to repeated administration of nicotine (Di-Franza & Wellman, 2007; Hamilton, Starosciak, Chwa, & Grunberg, 2012). Although behavioral studies have not firmly established a role for sensitization in the relapse to drug-seeking behavior, there is remarkable overlap in the underlying neurocircuitry (Steketee & Kalivas, 2011). Sensitization could serve as a useful model to determine the mechanisms by which repeated drug exposure alters brain function to enhance behavioral responses to drugs of abuse (Steketee & Kalivas, 2011).

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There are sex differences in the extent to which nicotine behavioral sensitization occurs, with female rats having greater nicotine behavioral sensitization than male rats (Harrod et al., 2004; Perna et al., 2008; Prus et al., 2008). This sex difference is consistent with reports of greater sensitivity to nicotine's effects on body weight, feeding, prepulse inhibition of the acoustic startle reflex, and antinociception in female rats than male rats (Chiari, Tobin, Pan, Hood, & Eisenach, 1999; Craft & Milholland, 1998; Faraday, Scheufele, Rahman, & Grunberg, 1999; Grunberg, Bowen, & Winders, 1986).

Enriched rat housing environments include physical stimulation (e.g., novel toys), social stimulation (i.e., the presence of other rats), or a combination of physical and social stimulation. Environmental manipulations have profound effects on rats' behavior and neurobiology (Hubel & Wiesel, 1970; Rosenzweig, Krech, Bennett, & Diamond, 1962; Simpson & Kelly, 2011). Neurobiological changes induced by EE include increased serotonin and dopamine neurotransmission in the prefrontal cortex (PFC; Brenes & Fornaguera, 2008; Zhu, Green, Bardo, & Dwoskin, 2004). On a behavioral level, EE results in reduced anxiety-like behaviors (Galani et al., 2007; Peña, Prunell, Dimitsantos, Nadal, & Escorihuela, 2006; Peña, Prunell, Rotllant, Armario, & Escorihuela, 2009), reduced depression-like behaviors (Brenes & Fornaguera, 2008), and increased learning (Brenes & Fornaguera, 2008). Most relevant to the present research, EE decreased reactivity to nicotine and nicotine behavioral sensitization in male rats (Coolon & Cain, 2009; Green et al., 2003).

Results of research comparing the effects of EE in male and female rats have been mixed (Bardo, Klebaur, Valone, & Deaton, 2001; Elliott & Grunberg, 2005; Zakharova, Starosciak, Wade, & Izenwasser, 2012). EE enhanced learning, social exploration, and exploration in a novel environment to a greater extent in males than in females (Elliott & Grunberg, 2005; Peña et al., 2006; Peña et al., 2009; Zakharova et al., 2012). However, hypothalamicpituitary-adrenal axis reactivity, anxiety, and prepulse inhibition were decreased to a similar extent in environmentally enriched male and female rats (Peña et al., 2009). There also were no sex differences in the effects of EE on the self-administration and actions of various drugs, including amphetamine and cocaine (Bardo et al., 2001; Zakharova et al., 2012). However, because there were sex differences in nicotine behavioral sensitization and in some behavioral effects of EE, it is possible that there may be sex differences in the effects of EE on nicotine behavioral sensitization

The present experiment was conducted to examine the effects of EE on nicotine behavioral sensitization in male and female rats. The selection of nicotine dosages in this research was based on previous research in which it was determined that 0.4-0.6 mg/kg nicotine was the optimal dosage to examine nicotine behavioral sensitization (DiFranza & Wellman, 2007). A dosage within this range, 0.5 mg/kg nicotine, was selected to examine the effects of EE on nicotine behavioral sensitization in the present research. Because it was possible that EE would shift the nicotine dose response curve to the right or left, dosages that were above (1.0 mg/kg nicotine) and below (0.1 mg/kg nicotine) the optimal 0.5 mg/kg nicotine dose were also included in the present experiment. Therefore, of the three dosages of nicotine selected, one was in the optimal range previously reported to elicit nicotine behavioral sensitization, and the others were below and above the optimal

dosages so that the effects of EE on a full dose-response curve of nicotine behavioral sensitization could be examined. The selection of days in which to examine locomotor activity was also based on recommendations by DiFranza and Wellman (2007). They report that the maximal response to nicotine usually occurs by drug Days 5–7. Because the effects of EE on nicotine behavioral sensitization were unknown, this period was expanded to include measurement on drug Days 9 and 12. Locomotor activity measurements were spaced 4 days apart to fall within the range of measurement intervals used in previous work from our laboratory (every 2 days; Hamilton et al., 2012) and others (every 7 days; Ericson, Norrsjo, & Svensson, 2010).

It was hypothesized that environmentally enriched male and female rats would have less nicotine behavioral sensitization than isolated rats. On the basis of previous reports of greater behavioral effects of EE in male rats (Elliott & Grunberg, 2005) it was hypothesized that EE would decrease nicotine behavioral sensitization to a greater extent in male rats than in female rats.

# Methods

#### **Overview**

The purpose of this experiment was to examine the effect of EE on nicotine behavioral sensitization in male and female rats. A 2 (Sex)  $\times$  3 (Housing Condition)  $\times$  4 (Drug Condition) full factorial design with repeated measures was used to examine effects of housing and drug condition in male and female rats. Nicotine behavioral sensitization was reflected by a statistically significant drug by time interaction paired with a pattern of increased open field locomotor activity over time in response to daily acute drug administration.

#### Subjects and Housing

Subjects were 144 Sprague-Dawley (72 male, 72 female) rats that were approximately 24–28 days old at the beginning of the experiment. There were six rats in each combination of the sex, housing, and drug dose variables (i.e., six rats per cell). Animals were housed on hardwood chip bedding (Pine-Dri) with continuous access to rodent chow (Teklad 4% Mouse/Rat Diet 7001) and water. Only rats of the same sex were housed together. The housing room was maintained at 23°C and 50% relative humidity on a 12-hr reversed light/dark cycle (lights on at 17:00) so that rats would be tested during their active (dark) phase.

Rats were housed in one of three conditions: isolation, social enrichment (three rats per cage), or combined physical and social enrichment (three rats per cage with novel toys). In the isolated condition, animals were housed individually in standard polycarbonate rat cages ( $40 \times 20 \times 20$  cm). In the enriched condition, animals were housed in groups of three in larger rat cages ( $46 \times 36 \times 20$  cm) with various toys (textured balls, rings, plastic bones, and plastic igloos) to provide physical and tactile stimulation. Objects were changed at least three times per week, or more frequently if damaged, to maintain a novel, physically enriched environment (Elliott & Grunberg, 2005; van Praag, Kempermann, & Gage, 2000; Varty, Paulus, Braff, & Geyer, 2000).

This experimental protocol was approved by the Uniformed Services University of the Health Sciences Institutional Animal Care and Use Committee and was conducted in full compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (NIH Pub, 82–23, rev. 1985).

### **Open-Field Locomotor Activity**

Open-field locomotor activity was measured using an Omnitech Electronics Digiscan infrared photocell system (Test box model RXYZCM [16 TAO]; Omnitech Electronics, Columbus, OH). Each rat was placed into a  $40 \times 40 \times 30$  cm clear Plexiglas arena, and locomotor activity was measured for 1 hr. In the photocell system, a grid of equally spaced infrared light beams traversed the plastic arenas ( $40 \times 40 \times 30$  cm) from front to back and left to right. When the infrared beams were broken, movement was recorded. Horizontal activity is the parameter that was analyzed in the present experiment. In this system, horizontal activity was quantified as the number of infrared beam interruptions or beam "breaks" in the horizontal sensor during the sample period. Data were automatically gathered and transmitted to a computer via an Omnitech Model DCM-I-BBU analyzer. During the drug administration phase, rats were placed in the testing chambers immediately after injections. Cage mates always were removed from the cage within 30 s of one another and tested at the same time in separate chambers.

## **Drug Administration**

Nicotine (0.1, 0.5, or 1.0 mg/kg) or physiological saline was administered via subcutaneous (SC) injections between the shoulder blades. Physiological saline was used as a vehicle for the nicotine solution. Solutions were pH adjusted to approximately 7.0 using Na<sub>2</sub>PO<sub>4</sub>. Nicotine solution was made from nicotine dihydrochloride and was expressed as nicotine base. All injections were 1 mL.

#### Procedure

The procedure included three phases: baseline, predrug, and drug administration. During the baseline phase, rats were housed individually, and in the predrug phase rats were housed in their assigned housing conditions. During the drug administration phase, rats were administered drug daily via SC injections and continued to be housed in the same condition in which they were housed during the predrug phase (see Figure 1).

**Baseline phase.** During the baseline phase, animals were housed individually in standard polycarbonate rat shoebox cages  $(42 \times 20 \times 20 \text{ cm})$ . All rats were briefly handled once each day for 2 days during this period to minimize stress that might occur as a result of handling during the experiment. All rats were placed in the locomotor chambers twice during the baseline period to acclimate them to the novel environment (Faraday & Grunberg, 2000). After the acclimation sessions, baseline locomotor activity was measured for the purpose of counterbalancing drug groups and housing conditions.

**Predrug phase.** After all animals were assigned to isolated (ISO), socially enriched (SE), or combined physically and socially enriched (PESE) housing conditions, they remained in these environmental conditions for 15 days. Locomotor activity was measured on predrug Day 4.

**Drug administration phase.** Animals were injected (SC) once each day with saline or nicotine (0.1, 0.5, or 1.0 mg/kg) for 12 days and open-field activity was measured for 1-hr immediately after injections on drug Days 1, 5, 9, and 12. Testing was conducted during the dark (active) portion of the cycle. Animals remained in their predrug phase housing condition during this phase of the experiment.

#### **Data Analytic Strategy**

During the baseline phase of the study (before rats were housed in their respective environments) locomotor data were analyzed using a univariate analysis of variance (ANOVA). Locomotor data from the predrug phase of the study (before nicotine or saline were administered) were analyzed using a univariate ANCOVA with baseline locomotor activity as the covariate. During the drug-administration phase of the experiment, locomotor activity data were analyzed using repeatedmeasures ANCOVAs with predrug Day 4 locomotor activity as a covariate. A significant day by drug interaction, coupled with a pattern of locomotor activity reflecting an increase over time, indicated that nicotine behavioral sensitization had occurred. When the assumption of sphericity was violated, a Greenhouse-Geisser correction was used. Multiple planned comparisons were controlled for using Bonferroni's correction. All statistical analyses were two-tailed, with an  $\alpha$  level of p < .05.

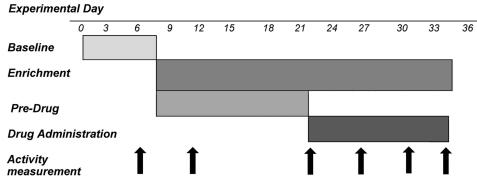


Figure 1. Timeline.

#### **Results**

#### Locomotor Activity in Males and Females

**Baseline phase.** Males had more locomotor activity than females (F(1, 125) = 5.71, p < .05). There were no significant differences among rats that later would be housed in different conditions or administered saline or various doses of nicotine (Figure 2).

**Predrug phase.** There were main effects of sex, F(1, 120) = 5.12, p < .05, and housing, F(2, 120) = 19.89, p < .001, on predrug Day 4 locomotor activity, as well as a sex by housing interaction, F(2, 120) = 6.51, p < .01. In male rats, ISO rats had more activity than SE rats and PESE rats. The activity of male rats housed in SE and PESE did not differ significantly. In female rats, there were no significant differences in the activity of rats housed in ISO and SE, but ISO rats and SE rats each had significantly more activity than PESE rats (Figure 2).

Drug administration phase. The occurrence of nicotine behavioral sensitization was indicated by a significant day by drug interaction, F(8.46, 341.04) = 20.71, p < .001, combined with a pattern of locomotor activity that increased over time in rats that received nicotine (Greenhouse-Geisser correction was used in this analysis; Figure 3). Overall, significantly less activity occurred on drug Day 1 than occurred on all subsequent drug days (drug Day 5: mean difference = -5,249.3, p < .001; drug Day 9: mean difference = -7,703.5, p < .001; drug Day 12: mean difference = -8,135.1, p < .001). In addition, less activity occurred on drug Day 5 than occurred on drug Day 9 (mean difference = -2,454.2, p < .001) or drug Day 12 (-2,885.7, p < .001). Activity increased significantly over time in response to all nicotine doses (e.g., within the 0.5 mg/kg dose, activity on drug Day 1 was significantly less than activity on drug Day 5 [mean difference = -9,472.2, p < .001], which was significantly less than activity on drug Day 9 [mean difference = -2,943.7, p < .05]), but activity did not increase over time in response to saline.

Nicotine behavioral sensitization was influenced by sex, as indicated by a significant day by sex by drug interaction, F(8.340, 319.715) = 2.072, p < .05 (Greenhouse-Geisser correction was used). Significantly more activity occurred in females than males

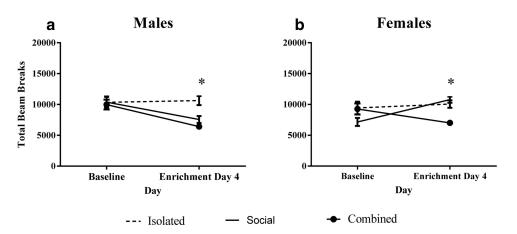
administered each nicotine dose on drug Day 1 (0.1 mg/kg: mean difference = 5,011.0, p < .01; 0.5 mg/kg: mean difference = 8,188.4, p < .001; 1.0 mg/kg: 6,171.8, p < .001) and in females than males administered 0.1 mg/kg nicotine on drug Day 12 (mean difference = 5,382.9, p < .01).

Nicotine behavioral sensitization was attenuated by housing in male and female rats, as indicated by a significant day by housing by drug interaction, F(16.91, 341.04) = 2.48, p < .01(Greenhouse-Geisser correction was used; Figure 4a-4d). For male and female rats that received 0.5 mg/kg nicotine, ISO rats had significantly more drug-induced locomotor activity than SE rats (mean difference = 6,562.8, p < .01) and PESE rats (mean difference = 7,634.7, p < .01) on drug Day 1. For male and female rats that received 1.0 mg/kg nicotine, ISO rats had significantly more drug-induced activity than SE and PESE rats on drug Day 9 (SE: mean difference = 8,525.1, p < .01; PESE: mean difference = 7.966.2, p < .01) and drug Day 12 (SE: mean difference = 9,735.4, p < .001; PESE: 10,170.6, p < .001). Drug-induced activity did not differ between SE and PESE on any drug day. Activity did not differ significantly among the sex and housing groups within the saline condition.

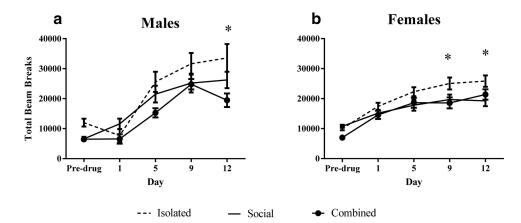
Because significantly more activity occurred in females than males administered each nicotine dose on drug Day 1 (0.1 mg/kg: mean difference = 5,011.0, p < .01; 0.5 mg/kg: mean difference = 8,188.4, p < .001; 1.0 mg/kg: 6,171.8, p < .001), additional analyses were conducted with drug Day 1 activity as a covariate. The effect of nicotine behavioral sensitization remained in males and females, as indicated by a significant day by drug interaction, F(5.4, 207.4) = 4.205, p < .01, but the attenuation of nicotine reactivity by housing condition became a nonsignificant trend (Greenhouse-Geisser correction was used).

## Discussion

In the present research, the effect of EE on nicotine behavioral sensitization was examined in male and female rats. There were several principal findings. First, male rats were more active than female rats at baseline. Second, before drug was administered, SE and PESE decreased locomotor activity in males whereas only



*Figure 2.* Locomotor activity on baseline day and enrichment Day 4 (mean activity  $\pm$  *SEM*) in isolation (ISO), social enrichment (SE), and combined physical enrichment and social enrichment (PESE) male rats (left panel) and in ISO, SE, and PESE female rats (right panel). The \* indicates an effect of housing, p < .01.



*Figure 3.* Nicotine behavioral sensitization on drug Days 1, 5, 9, and 12 collapsed across drug dose (mean activity  $\pm$  *SEM*) in isolation (ISO), social enrichment (SE), and combined physical enrichment and social enrichment (PESE) male rats (left panel) and in ISO, SE, and PESE female rats (right panel). The \* indicates an effect of housing, p < .01.

PESE decreased locomotor activity in females. Third, there was an effect of sex on nicotine reactivity, with females having greater activity than males on the first day of drug administration. Last, EE attenuated nicotine-induced locomotor activity in males and females, although this effect was diminished when controlling for the first day's locomotor activity. The finding that male rats had more locomotor activity at baseline than female rats was surprising given previous reports from our laboratory of similar baseline locomotor activity levels in Sprague-Dawley males and females (Elliott & Grunberg, 2005; Hamilton, Berger, Perry, & Grunberg, 2009). The finding that EE decreased open-field locomotor activity (i.e., increased habituation) in male and female rats before drug administration is consistent with previous research (Elliott & Grunberg, 2005; Varty et al., 2000). However, in females, the effect of EE on activity differed by type of enrichment. Although both types of EE (i.e., SE and PESE) decreased locomotor activity in males, only PESE, but not SE, decreased locomotor activity in females. Therefore, SE alone may not be sufficient to induce changes in habituation in female rats. For both sexes, exposure to novel environments induces a stress response in rats, a response that decreases as habituation occurs (Badiani et al., 1998; Rothwell, Kourrich, & Thomas, 2011). Although stress was not examined in the present research, it is possible that EE's effect to decrease stress reactivity (Garrido et al., 2013; Peña et al., 2009; Skwara, Karwoski, Czambel, Rubin, & Rhodes, 2012) underlies faster habituation in rats raised in EE. The finding that SE decreased locomotor activity in male rats, but not female rats, is interesting given that males had higher locomotor activity at baseline than female rats.

Nicotine behavioral sensitization occurred in male and female rats and was influenced by sex. The present finding is consistent with reports that female rats had greater nicotine behavioral sensitization than male rats (Harrod et al., 2004; Perna et al., 2008). In contrast, one study did not report sex differences in nicotine behavioral sensitization (Ericson et al., 2010).

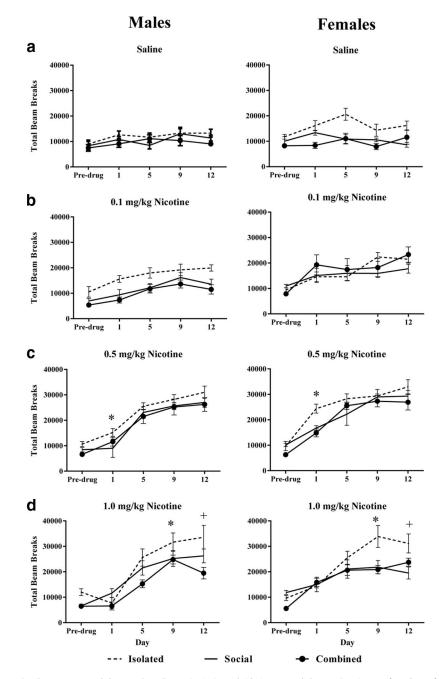
To our knowledge, we are the first to examine effects of EE on nicotine behavioral sensitization in female and male rats. In previous research, EE decreased reactivity to nicotine and nicotine behavioral sensitization in male rats (Coolon & Cain, 2009; Green et al., 2003). However, the present study found similar effects of EE on nicotine behavioral sensitization in female and male rats.

Although neurobiology was not examined in the present research, previous reports indicate that EE increased serotonin and dopamine neurotransmission in the PFC (Brenes & Fornaguera, 2008; Zhu et al., 2004) and increased dendritic arborization in two mesocorticolimbic structures relevant to drug reward—the ventral striatum (Comery, Stamoudis, Irwin, & Greenough, 1996) and the nucleus accumbens (Kolb, Gorny, Soderpalm, & Robinson, 2003). With respect to nicotine, EE increased medial PFC dopamine clearance after acute nicotine administration (Zhu et al., 2007). Future research might examine whether such neurobiological changes underlie effects of EE to decrease nicotine behavioral sensitization.

One limitation of this research is that estrous was not measured in female rats, and it is possible that estrous phase may have affected nicotine behavioral sensitization in female rats. Estrous cycle phase did not affect nicotine-induced activity or nicotine withdrawal in previous research from our laboratory (Elliott & Grunberg, 2005; Hamilton et al., 2009; Hamilton, Perry, Berger, & Grunberg, 2010). However, circulating sex hormone levels were associated with vulnerability and motivation for nicotine in adolescent male and female rats (Lynch, 2009). Future research should determine whether estrous cycle phase and circulating levels of sex hormones influence nicotine behavioral sensitization in male and female rats. A second limitation is that living in the ISO housing condition may have stressed the rats, a possibility that should be considered when interpreting the present findings.

#### Conclusions

Behavioral sensitization to nicotine occurs in male and female rats. EE has similar effects to alter nicotine behavioral sensitization in males and females. This research may have implications for understanding the directionality of the association between neighborhood disadvantage and smoking (Businelle et al., 2010) because it suggests that impoverished environments may augment



*Figure 4.* Locomotor activity on drug Days 1, 5, 9, and 12 (mean activity  $\pm$  *SEM*) as a function of group (isolation, social enrichment, and combined physical enrichment and social enrichment) and drug dose, with the left panels showing data for males and the right panels showing data for females. Each row shows the effects for each nicotine dose: (a) saline, (b) 0.1 mg/kg nicotine, (c) 0.5 mg/kg nicotine, and (d) 1.0 mg/kg nicotine. The \* symbol indicates an effect of housing, p < .001.

nicotine reactivity in men and women. Future research with rodents should examine physiological and neurobiological mechanisms underlying this association. These findings also have implications for smoking treatment and prevention strategies, particularly in individuals from underserved populations. Programs that incorporate aspects of social and environmental stimulation may have enhanced effectiveness in preventing and reducing cigarette smoking and may have implications for relapse prevention.

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